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Title:
The significance of withdrawal in a multidisciplinary profile of tobacco dependence

The significance of withdrawal in a multidisciplinary profile of tobacco dependence

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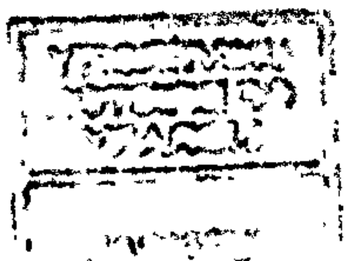
A dissertation submitted to the University of Bristol in accordance with the requirements of the degree of Ph.D. in the Faculty of Medicine.

Psychopharmacology Unit, Division of Psychiatry, March 2003.

Word count: sixty-two thousand
seven hundred and eighty six



ABSTRACT

The primary aim of this thesis was to increase understanding of the phenomenon of nicotine addiction. By combining cognitive, psychosocial, genetic and psycho-pharmacological data it was hoped we might achieve a more comprehensive understanding of models and mechanisms of smoking behaviour, and particularly the role of addiction and withdrawal in tobacco use and effect. The research also aimed to bridge the gap between psychology and pharmacology in the nicotine field. Experimental work conducted examined responses to nicotine withdrawal and reinstatement in humans in terms of mood and cognitive performance, and profiles personality and genetic characteristics that may influence the nicotine addiction phenomenon. The effect of noradrenergic drugs on tobacco dependence was also investigated, to examine how α2-adrenoceptor agonists can influence withdrawal. By generating a multidimensional tobacco "Addiction Index" score, it was possible to group smokers as addicted or non-addicted. Many of the chapters profile differences between these subgroups. For example, addicted smokers were significantly characterised by lower latency to first cigarette in the morning and accelerated reaction times following 24-hour smoking abstinence compared with non-addicted smokers. Addicted smokers were also more likely to report anxiety symptoms both as a personality trait and as a response to withdrawal than non-addicted smokers. Lofexidine, an α2-adrenoceptor agonist used successfully to manage opiate withdrawal; particularly the anxiety component, was shown to reduce overall severity of tobacco withdrawal symptoms and mitigate some of the performance deficits associated with tobacco withdrawal. Results indicate lofexidine could have a useful role either as an adjunct or alternative to nicotine replacement therapy.

ACKNOWLEDGEMENTS

To Anne Lingford-Hughes: Slave-driver, perfectionist, fundamentally negative reinforcer, fine upstanding proponent of the medical model, person with (incomprehensible) phobia of brackets, this can't have been easy for you either. Thanks for your durability and help where others fell by the wayside or spiralled off in a fractal of indifference.

To David Nutt and Andy Smith: Together you helped me embark on this voyage, and I have appreciated your guidance and encouragement along the way.

To Peter Rogers: Thank you for believing in my ability to work whilst finishing this thesis off. I hope I haven't let you down.

To David Ball: Much appreciation for your help with the DNA collection and analysis.

To Mel: I started this so that we could be together. Somewhere in the middle it helped drive us apart. You are still my one of my closest friends and most trusted allies, and I intend to present the finished article to you.

To Mike: I never knew real loss until you went away. I wish you could be here to share a celebratory glass of Madeira wine and a game of crib.

To Mummy and Daddy: Look! No hands! Thanks for being my indispensable stabilisers to the bitter end.

To other family and friends: I finished it, okay? So stop moaning. Yes, I will now have time to see you, talk to you, and communicate in a meaningful and non-distracted manner, and be less tetchy and self-absorbed. Well, everything is relative.

To tobacco: My inspiration and my nemesis. I'll fight you 'til the end, even though I will never know whether I've won.

AUTHOR'S DECLARATION

NAME ROBERT CHARLES HAYWARD
(in full, block capitals)

TITLE OF DISSERTATION THE SIGNIFICANCE OF WITHDRAWAL IN A MULTIDISCIPLINARY PROFILE OF TOBACCO DEPENDENCE

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Signed

Date 8/8/03

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LIST OF ABBREVIATIONS

5-HT: 5-hydroxytryptamine

ACh: acetylcholine

ANOVA: analysis of variance

BMDP: Bio-Mathematics Data Processing

CHIPS: Cohen & Hoberman Inventory of Physical Symptoms

CNS: central nervous system

CST: categoric search task

DNA: deoxyribonucleic acid

DOS: Direct Operating System (Microsoft)

DRDx: dopamine receptor Dx (where x is a number 1-5)

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Version Four

EEG: electroencephalogram

FAT: focused attention task

FTQ: Fagerström Tolerance Questionnaire

GABA: γ-aminobutyric acid

HPRU: Health Psychology Research Unit (University of Bristol)

ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision

ISEL: Interpersonal Support Evaluation List

LC: locus coeruleus

MHQ: Middlesex Hospital Questionnaire

nAChR: nicotinic acetyl choline receptor

NMDA: N-methyl-D-aspartate

NRT: nicotine replacement therapy

NS: Novelty Seeking

OWS: Other withdrawal symptoms

PCR: polymerase chain reaction

PET: positron emission tomography

POMS: Profile of Mood States

PPM: parts per million

PSS: Perceived Stress Scale

PTQ: Pre-test Questionnaire

QSU: Questionnaire of smoking urges

REM: rapid eye movement

RFS: Reasons For Smoking scale

RVIP: rapid visual information processing

SBI: Smoking beliefs inventory

SE: Self-esteem scale

SMQ: Smoking motivation questionnaire

SNI: Social Network Index

SPECT: single photon emission computed tomography

SPSS: Statistical Package for Social Scientists

SQB: Smoking questionnaire battery

SR: sustained release

SRI: Social Reaction Inventory

TCI: Temperament and Character Inventory

TPQ: Tri-dimensional Personality Questionnaire

UCLA: University of California Loneliness scale

VAS: visual analogue scale

VTA: ventral tegmental area

WHO: World Health Organisation

WSC: Withdrawal symptoms checklist

Chapter 1 – Introduction to tobacco addiction

1.1 Why study smoking?

Humans have used tobacco as a drug for approximately 2000 years. It is a native plant of the American continent, first introduced to Europe in the 15th Century. Although almost always smoked, the way tobacco is used has changed with time. In Britain, tobacco was smoked initially in pipes - particularly during the 16th and 17th Centuries. In the 19th century cigars became the most popular means of smoking tobacco, with cigarettes becoming the most preferred method in the 20th Century. The use of tobacco in Britain peaked in the years of 1945 and 1946 after World War II. It has been declining steadily since 1948, with 1998 U.K. smoking prevalence figures of 28% for men and 26% for women. There is some evidence that smoking prevalence is stabilising, although there is a worrying observed trend of increased prevalence figures in young women.

Current thinking suggests that unless cessation rates improve in line with these increases, we could witness the first increase of smoking prevalence for several years. Most smokers are first exposed to tobacco as children, with many going on to become habitual smokers. The mechanisms of smoking initiation are generally accepted to be social forces from peers, siblings, parents and teachers; these are all likely to contribute to the determination of whether a child will become a regular smoker, i.e. at least one cigarette per week (Rowe, Chassin, Presson, Edwards & Sherman, 1992). Other risk factors including socio-economic status and educational achievement also predict childhood smoker status. However, this thesis will concentrate on aspects of smoking persistence rather than initiation.

Cigarette smoking causes considerable mortality and morbidity - approximately 120,000 deaths each year in the UK. For example, in 1997 cigarette smoking accounted for 117,400 of the total of 628,000 deaths (Royal College of Physicians report, 2000). If these figures are representative, smoking contributes to 1 in 5 deaths in Britain. Although deaths related at least in part to smoking are due to a multitude of different conditions, three major disease states account for the majority of mortality: these are lung cancer, ischaemic heart disease and chronic obstructive pulmonary disease. Aside from these deaths, illness caused by smoking creates a major strain on the National Health Service, with many more non-fatal smoking-related hospital admissions and GP consultations on top of the 117,000 deaths. No other single avoidable cause of disease accounts for such a high proportion of deaths, hospital admissions or GP consultations.

Many physicians regard cigarette smoking as the single most important public health problem in Britain. It is also estimated that the difference in expenditure in one year (1996-1997) in England between non-smokers and smokers in terms of health care costs is £1,400 million. A further £328 million per year (based on 1991 figures) is suggested to be lost to the English economy as a whole due to smoking-related illness caused absence from work. Unfortunately there are no more recent figures than these regarding this feature of tobacco addiction, however it is likely that this total is now considerably higher.

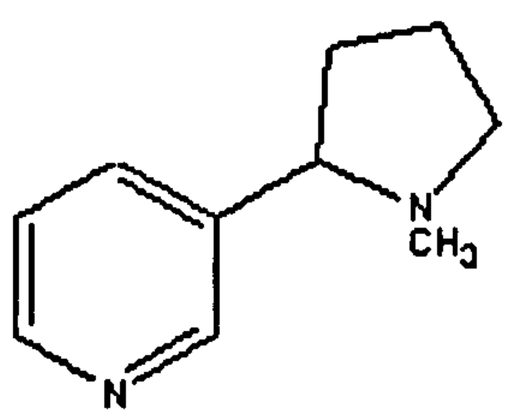
1.2 Psychopharmacology of nicotine

Why people smoke is both a challenging psychopharmacological problem as well as an issue of practical concern to health authorities. The pharmacology of nicotine is

now understood to be more complex than originally thought. Cigarette smoke is composed of volatile and particulate phases. Some 500 gaseous compounds including nitrogen, carbon monoxide (CO), carbon dioxide, ammonia, hydrogen cyanide and benzene have been identified in the volatile phase, which accounts for about 95% of the weight of cigarette smoke; the other 3500 compounds represent the 5% particulates (Ashton & Stepney, 1982). The most important particulate is nicotine. Other alkaloid particulates found in cigarette smoke include nornicotine, anatabine and anabasine. The particulate matter without its alkaloid and water content is called tar. Many carcinogens, including polynuclear aromatic hydrocarbons, N-nitrosamines and aromatic amines have been identified in cigarette tar.

It is the nicotine in tobacco that is accepted to be the major psychotropic substance, and is essentially responsible for the behavioural effects and addictive nature of smoking. Nicotine is a tertiary amine consisting of a pyridine and a pyrrolidine ring (left and right respectively in Figure 1.1). There are two stereoisomers of nicotine; *(S)-nicotine* is the active isomer that binds with *nicotinic acetylcholine receptors* (nAChRs), found mainly on cholinergic synapses, and is the naturally occurring alkaloid found in tobacco. During smoking, some racemisation takes place, and small quantities of *(R)-nicotine*, a weak agonist of cholinergic receptors, are found in cigarette smoke.

Figure 1.1 Molecular structure of nicotine



When inhaled in cigarette smoke, nicotine is quickly and efficiently absorbed from the lungs. Once in the bloodstream, nicotine is quickly distributed throughout the body, reaching the brain in approximately 15 seconds, where it is temporarily concentrated (Russell & Feyerabend, 1978). Thus inhaled puffs of cigarette smoke produce intermittent highly concentrated boli of nicotine in the blood – this factor is important in determining the actions of nicotine, since similar doses given more slowly produces different results in non-human subjects (Armitage et al. 1969). Nicotine is primarily metabolised in the liver, with an elimination half-life of approximately 2 hours (Benowitz, 1988). There are marked individual differences in the rate of metabolism, and the rate appears increased in chronic smokers. The question whether this is purely association or some causal link exists has driven examinations of genetic differences in cytochrome P450; these are enzymes mainly responsible for nicotine metabolism.

Some pharmacokinetic tolerance to nicotine develops in smokers, but pharmacodynamic tolerance is more important in determining smoking behaviour. Pharmacodynamic tolerance develops unevenly in smokers, who become tolerant to the emetic and irritant effects of nicotine but still exhibit tachycardia, rise in blood pressure, peripheral vasoconstriction, and endocrine and metabolic responses to smoking. Some aspects of tolerance appear to decrease rapidly: in chronic smokers the first cigarette of the day elicits greater cardiovascular responses than later cigarettes, and many smokers say that they get the greatest hedonic effects from the first daily cigarette (Ashton & Stepney, 1982; Royal College of Physicians, Tobacco Advisory Group, 2000).

As stated previously, nicotine's primary pharmacological target is the nicotinic acetyl choline (ACh) receptor. The drug exerts a biphasic, dose-dependent stimulant/depressant action on these receptors at cholinergic synapses. When puffs of cigarette smoke are intermittently inhaled, the time/dose relationship of nicotine reaching the brain can be such as to produce either stimulant or depressant effects. The initial combination of nicotine with the receptor stimulates a response, but persistent occupation of the receptors and prolonged effects on the neuronal membrane may block further responses (Rowell & Duggan, 1998). The degree of *stimulation versus block* depends on the amount of nicotine present relative to the number of receptors available. In general, small doses of nicotine produce principally stimulant effects at synapses and larger doses produce mainly depressant effects. At a high enough dose, nicotine can block synaptic transmission completely. This is fatal.

Thus, by varying factors such as the size of puff and depth of inhalation, a smoker can obtain predominantly inhibitory or predominantly excitatory effects, or a mixture of both, from one cigarette. The ease with which nicotine can produce rapid, reversible biphasic effects over a small dose range is probably a major factor determining and maintaining the popularity of the smoking habit, despite the well-publicised health risks (Ashton & Stepney, 1982). The variety of different effects of stimulation of nicotinic receptors may represent functions of the receptors at different locations, or different morphology of the receptors themselves. These effects are exerted on many brain systems including those involved in arousal, reward, learning, memory and attention (Pomerleau & Pomerleau, 1989).

1.3 Nicotinic receptors

Nicotinic acetyl choline receptors (nAChRs) are pentamers composed of five homologous membrane-spanning subunits around a central ion-channel that have distinct but overlapping expression patterns in subsets of neurons. Two α subunits and one each of β, γ and δ subunits (with a change during development from γ to ε) are arranged in the order αγαδβ. The two α subunits are the primary agonist binding subunits. Under normal conditions, opening of the ion channel results in an inward flux of Na^+ producing local depolarisation. After a brief period of being open, the nAChR goes through a series of conformational changes producing a *desensitised* state. In this configuration, the channel is closed to ions and is refractory to activation by agonist, although agonist can still bind to the receptor with low affinity. Low concentrations of agonist can push the receptor into the desensitised state without going through the open state (McGehee & Role, 1995). These properties have implications for the functional effects of nicotine during tobacco use.

Studies using techniques such as *in situ* hybridization and molecular cloning have revealed that multiple subtypes of functional neuronal nAChRs can be formed from various combinations of nAChR sub-units, with evidence to suggest that four functionally distinct receptor sub-types exist. The majority of high affinity nAChRs in the brain comprise the α4β2 sub-type (Zoli et al., 1998), though there are other subtypes present (heteromeric α3 and homomeric α7). Recent reports have attempted to associate pharmacological studies detailing the behavioural effects of nicotine with molecular and anatomical properties of nAChRs (e.g. Picciotto et al. 2000).

There is some evidence that mutant mice bred without the β2-subunit fail to derive reinforcement from self-administered nicotine, demonstrated by significantly faster extinction compared with wild-type mice (Picciotto et al. 1998). Further research shows serious problems associated with β2-subunit knockout mice; the cognitive deficits associated with ageing appear to be greatly accelerated, and there is evidence of depleted numbers of pyramidal neurons and neocortical hypotrophy (Zoli et al. 1999). It therefore appears that there is minimal, if any practical benefit achieved by targeting these nAChR sub-types, since the nicotinic system appears to suffer more generalised malfunctioning.

In comparison to muscarinic receptors, neuronal nAChRs are expressed in relatively low density in the human brain. In addition, their pattern of distribution is relatively homogenous and is not restricted to the well-defined brain cholinergic pathways. Studies using chicks and rats have characterised the neuroanatomical distribution of the various nAChR subtypes in these species, but there are few studies examining human nAChR distributions.

Attempts to examine these details have focussed on ligand binding studies showing distribution of nicotinic receptors, and *in situ* hybridisation techniques showing distribution of nAChR subunit mRNA in the human brain. Breese et al. (1997) and Hellström-Lindahl (1999) have concentrated on α7, α4, α3, β2 mRNA, with just one study examining α5 and β3 and β4 distribution in the post mortem human brain (Hellström-Lindahl et al. 1998). High levels of [3H] nicotine binding is found in thalamus, caudate nucleus and substanstia nigra, with moderate density found in frontal cortex parietal cortex and low density found in occipital cortex, temporal

cortex, hippocampus and cerebellum (Adem et al., 1987; Nordberg et al., 1988 and Perry et al., 1992).

Generally, exposure to agonists of a particular receptor produces down-regulation and exposure to antagonists produces receptor up-regulation, but this is not observed with nicotinic receptors. Research suggests that long-term exposure to nicotine results in increased numbers of nicotinic receptors in the brain of several species, including man. Post-mortem binding studies have shown increased [3H]nicotine and ACh binding sites in the brains of smokers compared to non-smokers with a dose dependent correlation observed between the number of cigarettes smoked and the increased number of binding sites (Benwell et al., 1988; Breese et al., 1997).

It is proposed that the desensitisation and up-regulation of nAChRs following chronic nicotine exposure is the basis of tolerance to nicotine displayed by smokers as well as being influential in producing withdrawal symptoms on cessation of smoking (Benwell et al., 1988; Balfour & Fagerstrom, 1996; Dani & Heinemann, 1996). The rationale behind nAChR up-regulation is thought to lie in their rapid desensitisation and consequent inaction following chronic agonist exposure, putatively resulting in a deficit in cholinergic function, which is then counteracted by an increase in receptor number (Schwartz & Kellar, 1985; Rowell & Duggan, 1998; Reitstetter et al., 1999).

There has been some imaging of nicotinic receptors with PET (Positron Emission Tomography) and SPECT (single photon emission computed tomography). These are both methods for imaging the regional distribution of radioactive tracers labelled with positron emitting radionuclides. These techniques have been successfully used to map

the binding and distribution of nicotinic receptors, allowing *in vivo* investigations. This is of considerable interest when examining involvement of these receptors in pathology of neuro-degenerative disorders like Alzheimer's and Parkinson's disease, and pathological conditions such schizophrenia, depression, epilepsy, and implication in neuropsychological processes such as learning and memory. It is hoped that studies of this nature may also provide insight into the neurobiology of nicotine addiction.

1.4 Effects of nicotine on brain activity

Electrophysiology studies have shown a variety of nicotine effects on brain activity. Small doses of intravenous nicotine or puffs of cigarette smoke introduced into the nostrils or lungs cause behavioural and EEG (electroencephalogram) arousal in sleeping animals (Hall, 1970; Domino, 1979). An ACh antagonist, *mecamylamine*, can block these EEG changes (Stolerman et al. 1973). Electrocortical arousal caused by cigarette smoke or intravenous nicotine in humans is accompanied by increased output of ACh from the cortex (Armitage et al 1969). Both smoking and intermittent intravenous shots of nicotine can also increase the magnitude of cortical evoked potentials (Ashton et al. 1980; Knott 1989).

Under certain conditions smoking and nicotine may decrease the level of arousal, providing further evidence for a biphasic action of the drug. Armitage et al. (1969) showed that some doses could cause slowing of EEG activity and a fall in cortical ACh output in anaesthetised cats. Mangan & Golding (1978) demonstrated in human smokers that under conditions of mild stress, induced by white noise, smoking increased the amount of slow alpha activity in the EEG. Ashton et al. (1980) found that the effect of nicotine on the slow cortical evoked potential was dose-dependent,

with small doses causing a stimulant effect but larger doses producing a depressant effect. These experiments demonstrate that smoking can both decrease and increase arousal, at least partly through its effect on cholinergic arousal systems.

There seems to be an interaction between dose, personality and environment that determines which effect predominates. Smokers can manipulate their nicotine dosage to obtain the desired effect in particular circumstances (Ashton & Watson, 1970; Ashton et al. 1974, 1980; Armitage et al. 1968). Smokers themselves report that the subjective effects of smoking can be either stimulation or relaxation, and there is considerable evidence (e.g. Ashton & Stepney, 1982) that smokers self-regulate their nicotine intake when smoking cigarettes of different strength.

1.5 Behavioural effects of nicotine

1.5.1 Nicotine effects on cognition

Although a large number of studies have examined the effects of smoking or nicotine on human cognitive performance, a number of issues need to be taken into consideration. Interpretation of these effects of nicotine depends on whether a study tests subjects who smoke under conditions of deprivation or non-deprivation. It is now understood that nicotine can reverse deprivation-induced impairments of mental performance (e.g. Heishman, Taylor & Henningfield, 1994), but true or absolute enhancement of performance can be demonstrated most effectively in non-deprived smokers or non-smokers (e.g. Heishman, 1998). These models of nicotine effect are often referred to as the "resource" model, purporting absolute benefits of nicotine, and the "withdrawal reversal" model, contending that nicotine only has positive effects relative to the impairments caused by tobacco withdrawal.

1.5.1.1 Nicotine effects on psychomotor performance

In general, smoking or nicotine produces motor activation, such that locomotor activity in tolerant animals is increased (Clarke & Kumar, 1983), and in non-smoking humans, finger-tapping rate is increased (West & Jarvis, 1986; Perkins et al. 1990). Perkins et al. (1994) reported that lower nicotine doses increased and higher doses decreased finger-tapping rate. Perkins et al. (1994) explained their finding of decreased response rate at higher doses by suggesting that elevated doses of nicotine cause blockade of peripheral ganglia.

Heishman & Henningfield (2000) argue that ganglionic blockade would be unlikely in the absence of overt signs of nicotine overdose. Heishman & Henningfield (2000) found that an 8 mg dose in nicotine gum impaired non-smokers performance on a 'circular lights' motor coordination task. They explain both their own and Perkins et al.'s (1994) findings as being secondary to increased dysphoria observed with giving non-smokers high doses of nicotine. However, Foulds, Stapleton, Swettenham, Bell, McSorley & Russell (1996) found no effect of subcutaneous injections of 0.3mg or 0.6mg nicotine on psychomotor performance in non-smokers. Perkins et al. (1994) also replicated earlier findings that finger-tapping rate is reliably increased by nicotine in overnight abstinent smokers. Research thus far therefore suggests nicotine has true positive effects on psychomotor performance.

1.5.1.2 Nicotine effects on attention

Nicotine has been shown to accelerate reaction time in abstinent smokers during tests of focused attention. Bates, Mangan, Stough & Corballis (1995) showed that smoking decreased decision time in a choice reaction time task in 2-hour deprived smokers.

Houlihan, Pritchard & Robinson (1996) reported nicotine producing faster reaction times in visual and auditory "oddball" tasks in 12-hour deprived smokers. Furthermore, a study of non-smokers showed that subcutaneous nicotine increased the number of fast reaction times (but not accuracy) in an information processing task (Le Houezec, Halliday, Benowitz, Callaway, Naylor & Herzig, 1994)

Nicotine has fewer robust effects on performance in tests of selective attention. It has been shown to reverse impairments on these tasks in deprived smokers (e.g. Heishman, 1994), but has few positive observed effects on non-smokers. The Stroop task (Stroop, 1935) is a classic test of distractibility. Studies using this task have examined abstinent smokers and non-smokers, and shown that nicotine either has no effect on performance (Foulds et al. 1996) or accelerated response time to both distracting and control stimuli (Perkins et al. 1994).

Nicotine has been most convincingly shown to improve performance in tasks requiring vigilance and sustained attention, particularly in tests of rapid visual information processing (RVIP) (e.g. Wesnes & Warburton 1984; Koelega, 1993). It has been shown that nicotine improves RVIP accuracy in abstinent smokers both by subcutaneous injection (Foulds et al. 1996) and cigarette smoking (Gilbert, Estes & Welser, 1997). Smoking has also been shown to increase processing rate in a subject-paced version of the task (Baldinger, Hasenfratz & Battig, 1995). In an early study, Wesnes & Warburton (1984) found improved RVIP performance in non-smokers following nicotine tablet administration. This has not been well replicated, although Foulds et al. (1996) reported faster reaction time and increased accuracy in non-smokers after subcutaneous nicotine.

Furthermore, nicotine has been shown to improve performance in non-smokers in a flight simulator (Mumenthaler, Taylor, O'Hara & Yesesage, 1998). In non-deprived smokers, subjects performing a driving simulation displayed decreased braking time and improved tracking following smoking. Warburton & Arnall (1994) reported that smoking a cigarette produced similar improvements in RVIP performance whether the smokers were deprived of nicotine for one or 12 hours, and similar results have been obtained using a nicotine patch (Warburton & Mancuso, 1998).

The modicum of evidence regarding several absolute performance-enhancing effects of nicotine is broadly consistent with animal studies (Mirza & Stolerman, 1998; Levin & Simon, 1998). In a recent study, Hahn, Shoaib & Stolerman (2002) found that nicotine improved accuracy and reduced omission errors and reaction times in rats on a five-choice serial reaction time task.

1.5.1.3 Nicotine effects on memory and learning

Learning and memory are affected by the level of arousal and appear to involve cholinergic pathways. Nicotine and smoking have been shown to affect some learning and memory processes in animals and man. For example, Coleman & Flood (1987) reported that nicotine improved memory consolidation, and Alpern & Jackson (1978) observed complex dose-dependent biphasic effects of nicotine on a variety of stages of the memory process in mice.

Armitage, Hall & Morrison (1968) found that nicotine could increase the rate of learning of reward or avoidance tasks in rats, depending on the dose and time after injection. In humans, the effects of smoking on learning and memory are complex,

dose-related and biphasic. Studies have shown that nicotine improved recognition memory in smokers abstaining overnight (Foulds et al. 1996; Perkins et al. 1994).

Early studies suggest smoking improves selective attention and memory consolidation, while not affecting or slightly impairing initial learning (Andersson, 1975; Mangan & Golding, 1978; 1983; Andersson & Hockey, 1977; Wesnes & Warburton, 1978; Williams, 1980; Ney et al. 1989). However, Rusted, Graupner & Warburton (1995) reported that smoking prior to list presentation enhanced word recall, whereas post-list smoking had no effect on intentional free recall.

Studies examining non-smokers showed that nicotine improved recognition memory dose-dependently (Perkins et al. 1994), and enhanced response time but decreased accuracy in a digit recall task (Foulds et al. 1996; Heishman & Henningfield, 2000). Recent research suggests that the observed memory enhancements following nicotine may be a bi-product of the attentional improvements. This theory is supported by findings that explicit effortful processing of material in the presence of nicotine is necessary for improved recall performance to be observed (Rusted, Graupner, Tennant & Warburton, 1998).

1.5.2 Nicotine effects on mood and arousal

Gross escalation of nicotine dosage does not occur in smokers. Since the rewarding effects of nicotine are probably derived from a combination of stimulant and depressant actions, and most smokers seek both these effects, they may be forced into maintaining a medium dosage, although addicted smokers are observed consuming between 10 and 80 cigarettes per day. This fine balance between stimulant and

sedative effects may contribute considerably to the tobacco habit. Subjects can obtain mild hedonic effects of the nicotine without the disruption of performance or after-effects that occur with other dependence-producing drugs. In fact, performance may be improved, as discussed above, and nicotine from cigarette smoke can be delivered in a controlled dosage to allow the subject to regulate his or her psychological comfort and performance in a way that is optimal in a range of environments (Ashton & Golding, 1989).

Mangan & Golding (1978) present an arousal modulation theory of smoking. They broadly proposed that smoking is an activity that has the function of controlling arousal, i.e. the smoker smokes to increase arousal when bored or fatigued, and to reduce arousal when tense or stressed. Their theory is an attempt to integrate these paradoxical biphasic psychological effects; that smoking can lead to either increased cortical arousal or to reduced stress and emotional calming (Ashton & Golding, 1989).

The effects of nicotine on electroencephalography (EEG) profiles are discussed in section 1.4, however they provide evidence that smoking can lead to heightened arousal (e.g. Church, 1989). In contrast, smoking deprivation leads to changes indicative of reduced cortical arousal (Knott & Venables, 1977). Smoking produces an array of sympathomimetic changes leading to heightened arousal including increased heart rate, vasoconstriction, raised blood pressure and increased serum adrenaline (Herxheimer, 1967; Domino, 1973; Hill & Wynder, 1974). The improvements to cognitive performance discussed previously could also be interpreted as evidence of heightened arousal.

Several questionnaire studies examining motives for smoking have found that many smokers report smoking for stimulation. These "stimulant" smokers report lighting up when they feel fatigued, bored or need to concentrate (Frith, 1971; Russell, Peto & Patel, 1974).

Evidence also exists that smoking can reduce subjective feelings of stress. Reviewing the effects of smoking on emotion, Gilbert & Wesler (1989) concluded that "nicotine reduces anxiety and negative affect in chronic smokers". When viewing a stressful film, smokers' ratings of anxiety were significantly lower when they were allowed to smoke than when they were not (Heimstra, 1973). Ikard, Green & Horn (1969) and Russell et al. (1974) performed questionnaire studies examining motivations for smoking, and one of the primary factors in the structures of both studies was for "sedative" smoking; i.e. smoking for stress or negative affect reduction. Approximately 80% of smokers report using cigarettes when they feel stressed or anxious (Russell et al. 1974; Warburton, 1988).

Other research has failed to find mood-enhancing effects of smoking or nicotine. Meliska & Gilbert (1991) examined overnight abstinent smokers changes in mood ratings over a morning when they smoked either five medium-nicotine or five nicotine-free cigarettes. Of the 19 scales they utilised only "drowsiness" showed significant improvement; nicotine cigarettes reduced these ratings compared with nicotine-free cigarettes.

The arousal modulation theory suggests that these psychological changes (increased alertness, decreased negative affect) are interdependent, with cigarettes sometimes being used to acquire one effect or the other. Thus, stimulant smokers tend to report smoking in order to increase arousal, while sedative smokers generally smoke to reduce feelings of stress or anxiety. "Sedative smokers, who smoke under conditions of high arousal in order to decrease arousal; and stimulant smokers, who prefer to smoke under conditions of low arousal in order to increase arousal" (Suraway & Cox, 1987).

Nicotine can stimulate the release of many different neurotransmitters implicated in mood and arousal, including glutamate, GABA, ACh, dopamine, noradrenaline and 5-HT (Lu, Marks & Collins, 1999; Wonnacott, Irons & Rapier, 1989; Grady & Marks, 1992; McGehee, Heath & Gelber, 1995; Marshall, Redfern & Wonnacott, 1997; Lu, Grady & Marks, 1998; Grady & Meinerz, 2001). Some of these effects potentially reduce activity in neuroanatomical structures associated with stress or anxiety (e.g. the locus coeruleus). Such an effect would tend to allay unpleasant subjective emotions such as anxiety, fear, frustration, and anger. Situations that give rise to these emotions have been shown to be those that increase the intensity of smoking in smokers. Schachter et al. (1977) noted an increase in the number of cigarettes under a high anxiety condition induced by electric shocks, and Mangan & Golding (1978) found an increase in the number and 'strength' of puffs when smokers were stressed by white noise. A similar relationship between stress and smoking intensity has been shown in questionnaire studies (e.g. Thomas, 1973).

Nicotine has been shown to attenuate the disruptive effects of stress on performance in several animal tests (e.g. Nelsen, 1978). Aggressive behaviour also appears to be modified by nicotine and smoking. Nicotine has been demonstrated to reduce aggressive behaviour in animals (e.g. Berntson et al. 1976), and Heimstra (1973) found that subjects allowed to smoke during a 6 hour vigilance task did not increase their ratings of aggression while deprived-smokers and non-smokers did. Additionally, Dunn (1978) reported that smoking prevented the disruption in performance caused by frustration in a complex perceptual motor task, although it is unclear whether these were both simply common elements of the tobacco withdrawal syndrome.

More recent research examining nicotine effects on anxiety and depression in both humans and animals suggests that the drug can be anxiolytic or anxiogenic depending on the anxiety model tested, the route of nicotine administration and the time course of administration (e.g. Picciotto, Brunzell & Caldarone, 2002). It is suggested that the broad expression of nAChRs throughout the brain, the large variety of nAChR subtypes and ability of nicotine to both activate and desensitise nAChRs explains the paradoxical effects of nicotine on emotional state (Picciotto et al. 2002).

Parrott (1998) challenges the view that arousal and emotional state are interdependent, citing psychological mood research (Mathews, 1990) showing that two distinct non-correlating factors emerge from standardised mood questionnaires; these were tense arousal (potentially representing negative affect) and energetic arousal (potentially representing positive affect). Parrott (1998) suggests it is perfectly normal for individuals to feel mentally alert and relaxed, or tired and irritated for example. It may

therefore be the case that by affecting different neurotransmitters or nAChRs nicotine can produce an array of simultaneous mood effects. In terms of negative affect reduction, it seems most likely however that the belief that smoking improves mood develops from the repeated experience of mood worsening during periods of abstinence (via nicotine withdrawal), rather than from a consistent effect of smoking improving mood above baseline (non-smoker) levels (Pomerleau & Pomerleau, 1990).

1.6 Definitions of terms associated with addiction

The terms "addiction" and "dependence" are essentially interchangeable in practice, and will be used interchangeably throughout this thesis. Under current definitions, the terms refer to "a situation in which a drug or stimulus has unreasonably come to control behaviour" (American Psychiatric Association, 1995).

The prevalent view of drug dependence holds that repeated exposure to certain psychoactive substances leads to neuroadaptations. These initiate a cycle of increasing tolerance and increasing self-administration until an asymptote is eventually reached (Alexander & Hadaway, 1982). Interruption of this cycle, by withholding the drug or alternatively blocking its action causes disequilibria, resulting in characteristic signs and symptoms, called a *withdrawal syndrome*, which can be relieved by taking the drug again. These symptoms should be temporary because after a period of sustained abstinence the body should revert to a "normal", drug-free state (West & Gossop, 1994).

In several ways, nicotine addiction fits this model very well. The development of smoking behaviour often follows a pattern of: initiation, followed by increased smoking, ultimately reaching a point where plasma nicotine levels are maintained (or "regulated") within characteristic limits according to the individual (Russell & Feyerabend, 1978). Pomerleau et al. (1983b) propose that once inaugurated, these patterns of smoking are extremely resistant to change, and when interrupted result in a powerful desire to smoke, and withdrawal.

Smoking to obtain nicotine meets standard diagnostic criteria for addiction. Comparable criteria for substance dependence in DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Version Four; American Psychiatric Association, 1995) and ICD-10 (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; World Health Organisation, 1998) both readily characterise tobacco dependence. The ICD-10 features: Strong desire to use the drug (potentially "craving"), difficulty in controlling use (difficulty cutting down or quitting), spending time obtaining, using or recovering from effects (although readily available, smokers often have to spend time somewhere specifically for smoking). Other ICD-10 criteria are: use of drug is given higher priority than other activities or obligations (this is less applicable to smoking), continued use despite harmful consequences (most smokers are aware of the health risks, hence their desire to stop (Freeth, 1998)), tolerance (manifested by absence of nausea or dizziness on use), and withdrawal (relieving this syndrome is a major motive for persistence; see later section). Hughes, Gust & Pechacek (1987) suggest the majority of smokers meet diagnostic criteria for tobacco dependence.

Given what is known about tobacco, it is unsurprising that a majority of individuals who smoke are dependent on nicotine and have considerable difficulty reducing or curtailing use (Hughes et al. 1987). However, 5% to 10% of the smoking population, referred to as tobacco "chippers", smoke fewer than five cigarettes a day, and these smokers do not exhibit characteristic features of nicotine dependence (Shiffman, 1989). This challenges traditional notions of drug dependence as an inevitable consequence of repeated exposures to an inherently addictive drug (Shiffman, 1991; Shiffman et al. 1994).

1.7 Neurobiology of nicotine addiction

Nicotine has reinforcing effects that have been demonstrated in animals. Specific doses enhance intracranial self-stimulation and animals will self-administer nicotine (Jarvik, 1967). In humans, smoking is reported to be pleasurable by nearly 90 percent of chronic smokers and has positive effects on mood, although it clearly does not produce a 'high' comparable with that of many other drugs of dependence. In addition it reduces pain and anxiety in stressful situations (Pomerleau et al. 1984). Hall & Turner (1972) demonstrated that nicotine increases the release of dopamine and noradrenaline from limbic areas and the hypothalamus in animals; these phenomena may be the basis for its rewarding effects. In addition, nicotine may interact with opioid reward systems (Karras & Kane, 1980), and smoking has been shown to increase plasma concentrations of beta-endorphin-beta-lipotrophin in humans (Pomerleau et al. 1983a).

As discussed below, the dopamine system has been strongly implicated in nicotine addiction, but is not believed to be exclusively responsible for the behavioural effects

of nicotine. Animal studies involving microinjections to other brain structures have elicited behaviours associated with nicotine addiction (e.g. Iwamoto, 1990), though there may be indirect involvement of mesolimbic dopaminergic sites. Whether a unitary circuit mediates addictive behaviours observed with nicotine or whether multiple mechanisms exist via selective neuroanatomy has not been adequately addressed. It is also unclear whether actions of nicotine at a single high-affinity binding site can account for all its behavioural and addictive effects.

1.7.1 'Dopamine hypothesis' of nicotine addiction

Nicotine is a powerful reinforcer, which may be due to its indirect stimulation of dopamine release (Reavill, 1990). The discovery of nicotinic receptors in the ventral tegmental area (VTA) of the mid-brain, which activates the ascending mesolimbic dopamine system, was an important finding in understanding the neurobiology of nicotine addiction (Nisell et al., 1994a; 1994b). Small concentrations of nicotine, similar to those in the plasma of cigarette smokers, selectively enhance the release of dopamine in the nucleus accumbens *in vitro* (Rowell et al. 1987). Studies using microdialysis and voltammetry have reported similar effects in the nucleus accumbens *in vivo* after systemic administration of nicotine (Imperato et al. 1986; Brazell et al. 1990). Dopamine is released when nicotine is infused directly into the nucleus accumbens (Mifsud et al. 1989). The receptors involved may correspond to the high-affinity binding site for nicotine, and the lack of tolerance to the effect suggests it may be relevant to the positive reinforcing and discriminative stimulus properties of nicotine.

All drugs of abuse appear to stimulate dopamine release in the shell area of the nucleus accumbens rather than the core (Pontieri et al. 1996; 1998). Nicotinic receptors are located on both the terminal membranes in the nucleus accumbens and on the cell body membranes of the dopamine-secreting neurons in the mid-brain that innervate the nucleus (Clarke & Pert, 1985). There is evidence that responses to nicotine injections (either intravenous or subcutaneous) are predominantly mediated by the receptors located on the cell bodies in the mid-brain, although receptors on terminals may also contribute to resultant dopamine release (Benwell et al. 1993).

Nicotine self-administration in animals is significantly attenuated by dopamine antagonists (Corrigall & Coen, 1991) and by lesions of dopamine-containing neurons of the nucleus accumbens (Corrigall et al. 1992). As discussed previously, there is evidence that mice lacking the β2 subunit of the nicotine receptor are impaired in terms of both operant nicotine self-administration patterns and subsequent dopamine release. These findings are evidence that nicotine's action on dopamine pathways is a major contributor to nicotine self-administration.

Addiction is widely accepted to be a result, in part, of chronic or repeated exposures to a drug. Therefore the ways in which brain responses are influenced by chronic exposure may be essential to understanding the neurobiology of addiction. Animal studies using *in vivo* microdialysis have suggested that repeated administration of amphetamine or cocaine results in sensitisation to their effects on dopamine release in the nucleus accumbens (Kalivas et al. 1993). Robinson & Berridge (1993) have postulated that this sensitisation may have a central role in the development of addiction; particularly that sensitisation of the pathway may facilitate the way in

which behaviours associated with obtaining the drug are learned, and with the process by which 'drug-liking' becomes 'drug-wanting'. The latter term may represent what is commonly referred to as "craving".

Crucially, repeated injections of nicotine have also been demonstrated to result in sensitisation of effects on dopamine release in the nucleus accumbens (Benwell & Balfour, 1995). The mechanisms underlying this sensitisation response to repeated exposure are yet to be clearly defined. It would appear co-stimulation of the NMDA glutamatergic receptor is involved, since both the development and expression of the sensitised dopamine response are attenuated or abolished by the administration of NMDA receptor antagonists (Shoaib et al. 1994; Balfour et al. 1996). Co-stimulation of NMDA receptors has also been implicated in the mechanisms underlying sensitisation to other psychostimulant drugs of abuse, and is probably associated with an increase in the burst firing of neurons (Kalivas et al. 1993; Overton & Clark, 1997).

Neurochemically selective 6-hydroxydopamine lesions of the mesolimbic dopamine system weaken both the self-administration and the locomotor activity produced by nicotine in rats. Dopamine receptor antagonists selective for the D1 receptor can block *place preference* (a drug-seeking behaviour test technique) produced by nicotine, although this has not been demonstrated conclusively (Acquas et al. 1989). Microinjection studies show that the nucleus accumbens may also mediate other effects such as locomotor activation or depression (e.g. Welzl et al. 1990). Reavill & Stolerman (1990) found that nicotine increased locomotor activity when infused into

the ventral tegmental area; further evidence for the involvement of the mesolimbic dopamine system.

The above research examining the role of mesolimbic dopamine pathways in nicotine addiction are almost entirely based on animal studies. There is some circumstantial evidence that the conclusions also apply to the reinforcing effects of nicotine in tobacco smoke, in that administration of haloperidol, a dopamine antagonist, increases smoking in habitual smokers (Dawe et al. 1995). Furthermore, bromocriptine (a D2/D3 dopamine agonist) has been shown to reduce the mean duration of puffs, number of puffs and number of cigarettes smoked. Subjects receiving bromocriptine also reported less craving for cigarettes (Jarvik et al. 2000a).

Mecamylamine blocks the effects of ACh at nicotinic receptors and also blocks the positive reinforcing effect of nicotine in humans and animals. Correlations have been reported between the ability of drugs to produce the nicotine discriminative stimulus (a behavioural science technique aiming to induce selective operant conditioning), and their action at the high-affinity binding site for [^{3}H]nicotine, although ligand-binding studies have not directly correlated the reinforcing effect with action at central nicotinic receptors.

It is important to remember that tobacco-smoking habits are heterogeneous and that people smoke cigarettes at varying frequencies and in different ways. Regular smoking results in the accumulation of nicotine in blood plasma during the 'smoking day'. The nicotine levels fall during sleep as the drug is metabolised and cleared from the body (e.g. Benowitz et al. 1987). Prolonged exposure to nicotine has been shown

to cause desensitisation of many of the neuronal nicotinic receptors. Pidoplichko et al. (1997) have demonstrated that plasma concentrations of nicotine commonly found in habitual smokers during the day are sufficient to desensitise nicotinic receptors on the mesolimbic dopamine neurons. As a result, the administration of a nicotine bolus no longer causes increased dopamine in the nucleus accumbens (Benwell et al. 1995).

These findings create significant problems for the 'dopamine hypothesis' of nicotine addiction. They suggest that many smokers may continue smoking under conditions whereby nicotine is unlikely to stimulate the mesolimbic dopamine neurons, and that other neural mechanisms must presumably also contribute to the 'rewarding' properties of the drug that reinforce addiction. For those who smoke infrequently, significant peaks and troughs of nicotine levels may be observed (Russell, 1990). If nicotine concentration in the 'trough' falls below that required to desensitise the nicotinic receptors on mesolimbic dopamine neurones, each cigarette will be rewarded with increased dopamine release. For these smokers, stimulation of dopamine release is likely to be the predominant mechanism underlying addiction to nicotine.

Non-addicted smokers or chippers (q.v.) may therefore receive a greater acute dopamine effect from tobacco smoking than addicted smokers. This would clearly present problems for a definitive dopamine hypothesis of tobacco dependence. The motivating factors for the two groups may therefore be very different psychopharmacologically. Potentially addicts generally smoke in order to avoid withdrawal effects, or literally smoke "automatically"; i.e. it has become a stereotyped motor behaviour.

1.7.2 Noradrenaline and nicotine addiction

Nicotine has been shown to both increase and decrease noradrenergic activity. It is suggested that increased noradrenaline following nicotine administration is partly responsible for the stimulant effects of the drug. Conversely, receptor desensitisation occurring on noradrenergic neurons may contribute to the subjective anxiolytic experience of smoking.

It has been argued that receptor desensitisation may be the response that is reinforced in frequent or heavy smokers (Balfour & Fagerström, 1996). For example, nicotinic receptors located on noradrenaline-secreting neurons are desensitised by nicotine concentrations comparable to those found in the plasma of many smokers (Benwell & Balfour, 1997). This may contribute to the tranquillising properties of tobacco smoke often reported by smokers exposed to environmental stressors. Since nicotine exerts its effects by acting at a family of nicotine receptors, it is possible that other neural responses, mediated by receptors more resistant to desensitisation may also play a role in nicotine addiction.

Wonnacott (1990) describes animal studies that demonstrate an increase in high-affinity receptor density when they are chronically exposed to nicotine levels large enough to cause a desensitisation of catecholamine responses to the drug. This increased density seems to reflect a decreased turnover of the receptor complex (Marks et al. 1992; Peng et al. 1994), however the psychopharmacological significance of this effect remains unclear. It is unlikely that the increased receptor density accounts for the desensitisation to nicotine discussed above because up-regulation of the receptors is not observed with dosing regimens that elicit the

sensitised dopamine responses (Benwell & Balfour, 1985). The increase in receptor density may still be significant to the mechanisms underpinning nicotine addiction since they are also observed in brain tissue taken from humans who have been habitual smokers (e.g. Benwell et al. 1988).

Bupropion, an atypical anti-depressant prescribed for aiding smoking cessation has both dopaminergic and noradrenergic actions. Clonidine, an α2-adrenoceptor agonist has also been found to be effective in helping to quit smoking. The effects of these drugs in reducing noradrenergic activity may be reducing the intensity of the withdrawal syndrome, perhaps in a similar way to anti-noradrenergic treatments of opiate withdrawal (Gourlay & Benowitz 1995) (see section 1.7.2).

If nicotine does have true calming or anxiolytic effects, some of the above treatments may also replace the putative direct effects of nicotine on noradrenergic systems. However, most experimental work would predict the opposite effect. Animal studies using microdialysis demonstrate that nicotine administration into the cerebral aqueduct leads to dose-dependent increases in noradrenaline levels in the hypothalamus, resulting in increases in levels of stress hormones (Sharp & Matta, 1993; Fu et al. 1997). Systemic administration of nicotine also results in increased levels of noradrenaline in the amygdala and hippocampus (Fu et al. 1998), limbic structures known to regulate central mechanisms affecting stress hormone response (Feldman & Weidenfeld, 1996). Clarke & Reuben (1996) report that nAChRs that mediate noradrenaline release are pharmacologically distinct from those that mediate dopamine release.

The locus coeruleus (LC) is a structure rich in noradrenaline-secreting neurons and implicated in fear and anxiety responses. Léna et al. (1999) investigated nAChRs distribution in LC and found two types of neurons in this body expressed different receptor subtypes. Type A LC cells, that are small in size but have large nicotinic currents expressed α3 and β4 subunits. Type B cells, corresponding to the predominant noradrenergic projection neurons to the hippocampus, express β2, α4, α6 and β3 subunits. Léna et al. (1999) also found α5 and α7 subunits expressed in LC neurons. Their study suggests that nicotine can activate Type A and B cells with differential kinetic and desensitisation properties. This may explain some of the paradoxical effects of nicotine in terms of mood, arousal and withdrawal effects.

Post-mortem studies demonstrate a relationship between chronic nicotine use and changes in noradrenergic neurobiology. Klimek et al. (2001) compared LC tissue radioligand binding in long-term smokers and non-smokers. They found that binding to α2-adrenoceptors was significantly lower along the axis of LCs of long-term smokers compared to non-smokers. They interpret their data as showing that long-term smoking down-regulates α2-adrenoceptors in the LC. They also comment that putative smoking-induced effects are widespread in the LC and not delimited to a specific sub-region, suggesting extensive effects of cigarette smoking on noradrenergic activity in the CNS. As the authors conclude, however, it is not possible to assert whether smoking actually causes these down-regulations in α2-adrenoceptors or whether a relative paucity of these receptors, possibly genetically mediated, predisposes individuals to tobacco addiction.

1.7.3 Chronic nicotine administration and 5-hydroxytryptamine

Anxiety is a withdrawal effect of nicotine abstinence, and believed to be mediated, at least in part, by 5-hydroxytryptamine systems. Animal studies suggest that chronic nicotine exposure causes repeated or prolonged reductions in demand for 5-HT in the hippocampus (Benwell & Balfour, 1979) by reducing the concentration and ability to synthesise 5-HT in appropriate terminals in the structure (Benwell & Balfour, 1982; Ridley & Balfour, 1997).

Human post-mortem studies have shown that habitual smoking is associated with a regionally-selective reduction in the concentration of 5-HT and its principal metabolite, 5-hydroxyindole acetic acid, in the hippocampus; this is not observed in a majority of the other areas of the brain that have been studied (e.g. Benwell, Balfour & Anderson, 1990). Comparing this with the animal data, it seems reasonable to suggest that nicotine in tobacco smoke mediates a reduction in formation and release of hippocampal 5-HT.

Again, the consequences of these changes in hippocampal 5-HT elicited by nicotine remain to be determined. Studies have suggested that increased stimulation of 5-HT receptors in the hippocampus may be implicated in anxiety (Andrews et al. 1994), and it could be that this mechanism is involved in the decreases in anxiety consistently reported by smokers following tobacco use. Nicotine has reported anxiolytic properties in some tests (Brioni et al. 1994), although these findings have been contested (Balfour, Graham & Vale, 1986). If this hypothesis is correct, increases in receptor density could contribute to the symptoms often observed during the early stages of smoking cessation; i.e. acute tobacco withdrawal. Under conditions of initial

abstinence, hippocampal 5-HT release will no longer be suppressed, possibly resulting in feelings of anxiety.

Other reports implicate occupation of the 5-HT_{1A} receptor subtypes in the expression of the glucocorticoid receptors, which exert an inhibitory effect on pituitary-adrenal activity (Seckl & Fink, 1991); these are psychobiological mechanisms by which we cope with the stresses of everyday life (Benwell & Balfour, 1982). It can be argued therefore that effects of chronic nicotine on hippocampal 5-HT include attenuation of the mechanism that mediates adaptation to environmental stress, and upon acute cessation mediate certain tobacco withdrawal effects such as anxiety and depression (Fagerström & Schneider 1989).

1.7.4 Nicotine addiction and other neurotransmitters

As stated earlier, nAChRs are found on many neurons throughout the CNS. These pathways include many of the acetylcholine-secreting neurons found in the hippocampus and cortex. Nicotinic receptors are also found on terminals that secrete the excitatory amino acid, glutamic acid, and the inhibitory amino acid, γ-aminobutyric acid (GABA) (Wonnacott et al. 1990; McGehee et al.1995; Lu et al. 1998). The behavioural consequences of the action of nicotine on these neurons remain to be established. Stimulation of the receptor located on glutamate-secreting terminals facilitates release of the transmitter (McGehee et al. 1995).

Stimulation of the NMDA receptors located on the dopamine-secreting neurons in the VTA results in increased burst firing of those neurons, and thus an enhanced dopamine response to nicotine (Balfour et al. 1998; Schilström et al. 1998). It is well

accepted that the effects of nicotine on cholinergic neurons are implicated in increased arousal and attention sometimes associated with smoking (e.g. Balfour, 1984). Additionally, stimulatory effects of nicotine on acetylcholine and glutamate secretion in the hippocampus and cerebral cortex may mediate the reported improved cognitive function (Balfour & Fagerström, 1996). Smokers have long cited nicotine's apparent positive effects on cognition as a reason why they smoke.

1.7.5 The tobacco withdrawal syndrome

Cessation of smoking can give rise to a definite abstinence syndrome (Jaffe, 1980; Hatsukami et al. 1984). It cannot be labelled a "nicotine withdrawal syndrome" since it is difficult to demonstrate that it cannot occur through the loss of other aspects of smoking. Alternatively, it has not been demonstrated to occur with acute cessation of use of nicotine replacement products (e.g. nicotine gum).

In keeping with the biphasic effects of nicotine, this syndrome shows characteristics of the withdrawal reaction from both stimulant and depressant drugs. Withdrawal effects include craving for tobacco, nausea, headache, constipation, restlessness, decreased psychomotor performance, increased appetite and weight, lethargy, depression, irritability, anxiety, restlessness, decreased cognitive and psychomotor performance, increased low frequency EEG activity, and fall in blood pressure and heart rate. The syndrome starts within 24 hours of smoking cessation and some symptoms may persist for many months. However, the severity is variable and some smokers can give up without difficulty.

Unsurprisingly, the severity of the withdrawal syndrome is related to the pre-cessation smoking levels and profiles, with more frequent and more dependent smokers experiencing relatively greater discomfort (West & Russell, 1985; Hughes & Hatsukami, 1986). The symptoms may be partially alleviated by nicotine replacement therapy (Russell et al. 1980; Pomerleau & Pomerleau, 1988; Gross & Stitzer, 1989), but the relapse rate of smokers advised to stop smoking for health reasons or attending anti-smoking clinics is high.

Craving for tobacco is commonly increased under conditions of abstinence from smoking (Shiffman & Jarvik, 1976; Hughes & Hatsukami, 1986). There is little consensus regarding a definition of craving. An Expert Committee meeting on drug craving convened by the United Nations and World Health Organisation defined drug craving as "the desire to experience the effect(s) of a previously experienced psychoactive substance". This definition is considered to accurately describe the phenomenon of drug craving in humans and can thus be clinically useful (Markou et al. 1993).

Theories regarding cigarette cravings are consistent with general models of drug craving; they assume that urges and cravings represent subjectively experienced motivational states that are responsible for ongoing drug use in drug-dependent individuals, and precede and precipitate relapse episodes in addicts attempting abstinence (Shiffman, 1979; West & Schneider, 1987). Instruments such as the Questionnaire of Smoking Urges (Tiffany & Drobes, 1991) have been devised to characterise and quantify levels of tobacco craving.

The inclusion of "craving for tobacco" in the tobacco withdrawal syndrome is contentious, fundamentally because smokers crave tobacco when non-deprived, and even whilst smoking. The case is made for the inclusion of this symptom by evidence demonstrating these cravings are reduced by nicotine replacement (Russell et al. 1993) and correlate with other elements of the syndrome (Zinser et al. 1992). Craving for tobacco is often regarded as the most important factor in the withdrawal syndrome, since it is the most predictive of subsequent relapse to smoking (West, Hajek & Belcher, 1989; Swan, Ward & Jack, 1996).

Anxiety is a distressing negative emotional state that may have multiple components. Smokers' subjective ratings of anxiety are frequently increased following abstinence (Hughes & Hatsukami, 1986; Hughes, Higgins & Bickel, 1994). The nature of the abstinence is likely to be important to the validity of this symptom, as discussed below. Anxiety associated with acute tobacco withdrawal may be a direct result of the elimination of nicotine from the CNS. This may be due to consequent effects on neurotransmitter systems that have adapted to an environment whereby the drug is regularly administered. This is likely to be experienced most severely by highly dependent smokers who have higher blood nicotine levels and greater nicotine tolerance. Alternatively, psychological disturbances caused by changes in behaviour may mediate increases in anxiety.

There is also ongoing debate as to whether anxiety should be included as a symptom in the withdrawal syndrome. West & Hajek (1997) propose that it should not, as they found that anxiety levels fall rather than rise among totally abstaining smokers (as opposed to those who might have had minor lapses). Other studies have reported an

initial elevation in reported anxiety after stopping smoking, but this is short-lived and followed by a reduction to below anxiety levels while smoking (Hughes et al. 1994). Furthermore, West & Hajek (1997) argue that increased anxiety observed in earlier studies on smoking cessation is a psychological response to the attempt to stop, which is worsened when that attempt is not wholly successful.

1.8 Treating tobacco dependence

There are a variety of different approaches to managing nicotine addiction. These can broadly be categorised as population interventions (advertising or educational campaigns, brief routine interventions by health-care professionals, over-the-counter products, etc.) or individual interventions (intensive expert-delivered treatments). The two approaches overlap, and there are regular efforts made to adapt those interventions effective in the intensive treatment setting to the wider-reaching management strategies. For the purposes of this introduction, however, it is more appropriate to categorise methods of smoking management as either pharmacological or non-pharmacological.

1.8.1 Non-pharmacological treatments aiding smoking cessation

Due to the scale of smoking prevalence, there is a need for interventions to reach large populations. Various interventions have been attempted, such as community-level poster, self-help and competition campaigns. More general self-help literature is available, updated to include current advice about nicotine-replacement therapy (NRT), and this is shown to be modestly more effective than no intervention (Lancaster & Stead, 2000). Telephone help-lines have also been shown to be effective at improving quit rates (Zhu et al. 1996), as have brief advisory interventions by

healthcare professionals such as general practitioners or nursing staff (Cromwell et al. 1997; Silagy & Ketteridge, 1999). Many of these generic non-pharmacological approaches are only effective in treating light smokers rather than more dependent smokers (e.g. Jackson et al. 1986).

Smoking cessation clinics in the UK usually offer a combination of NRT and behavioural support. Importantly, well-organised intensive treatments are effective in helping even highly dependent smokers to stop smoking for a period of several weeks. The efficacy of intensive behavioural interventions is enhanced when an element of social support is prominent (West, Edwards & Hajek, 1998). Ways of designing, evaluating and implementing social support treatments on a larger scale could be an extremely cost-effective means of improving overall smoking cessation rates.

Hypnosis and acupuncture are popular approaches to quitting smoking. Studies investigating hypnosis and acupuncture for smoking cessation have concluded that specific efficacy is lacking, but individuals may be helped by placebo or non-specific effects (Abbot et al. 1999; White & Rampes, 1999).

1.8.2 Pharmacological treatments aiding smoking cessation

NRT and the atypical antidepressant bupropion (Zyban®) are the only pharmacotherapies licensed in the UK to treat nicotine addiction. This is because these drugs have been reliably shown to improve cessation rates and have minimal side effects. Clonidine, an α2-adrenoceptor agonist, and mecamylamine, a non-competitive nAChR antagonist, have also been studied as treatments for smoking cessation either alone or as adjuncts to nicotine patches.

1.8.2.1 Nicotine replacement therapy (NRT)

The key difficulties acutely experienced by smokers attempting cessation seem to be attributable to the tobacco withdrawal syndrome. NRT essentially breaks the quitting process into two phases; in the first phase, quitters learn to cope without smoking behaviour and regular rapid boli of nicotine, while putatively protected from the worst withdrawal effects by moderate levels of nicotine afforded by NRT. Once this adaptation has developed, nicotine is gradually withdrawn completely.

NRT alleviates withdrawal discomfort (Russell, 1990). In a recent review, West & Shiffman (2001) reviewed 27 studies investigating oral NRT device (gum, inhalator, tablet) effects on withdrawal symptoms and craving in abstinent smokers. They concluded that oral NRT reduces total withdrawal discomfort, and particularly anxiety and irritability. They found modest evidence for NRT effects on depressed mood and craving, although gum was less effective than other devices in reducing craving. Nicotine patches and nasal spray have also been demonstrated to mitigate withdrawal discomfort and the severity of craving/urges to smoke (Fagerström et al 1993; Pickworth et al. 1996; Sutherland et al. 1992; Leischow et al. 1997).

Although this comprises the main effect of NRT, other mechanisms may have a role, such as the provision of a coping mechanism, or possibly replacing some of the hypothetical positive effects of nicotine, such as increased alertness (West, 1992). NRT may also make early relapses to smoking in quitters less rewarding, and therefore less likely to trigger a full-scale relapse. A related possible mechanism could be deconditioning because the link between pharmacological reinforcement and smoking behaviour may weaken during abstinence accompanied by NRT use.

NRT can be administered via patches, gum, inhalators, nasal sprays, sub-lingual tablets and lozenges. These are available in different strengths and versions, and different products and potencies are indicated for different individual smokers.

Irrespective of the particular device or product, NRT is reliably shown to help smokers quit. In a recent review, the overall odds ratio for abstinence with NRT compared to placebo was 1.73 (Silagy et al. 2000). In addition to enhancing early cessation, there is evidence that NRT also reduces early relapse (Stapleton et al. 1995).

Increasing dose seems to increase treatment efficacy, though the dose-response curve is shallow; for example, 4mg nicotine gum was shown to be more effective than 2mg gum in highly dependent smokers (e.g. Hughes et al. 1999b). Small but significant advantages have been demonstrated in 25mg over 15mg patches in sustained one-year abstinence rates (Tonnesen et al. 1999).

1.8.2.2 Bupropion (Zyban®)

The evaluation of use for antidepressants in smoking cessation pharmacotherapy (Covey et al. 2000) stems from the observed association between smoking, smoking cessation and depression (Breslau, Kilby & Andreski, 1993). Initial observations that depressed smokers administered the antidepressant bupropion experienced reduced craving for tobacco (Ferry & Burchette, 1994) led to larger trials examining the tolerability and efficacy of a sustained-release (SR) formulation of the drug as a smoking cessation agent (Hurt et al. 1997; Jorenby et al. 1999).

Bupropion SR has been consistently demonstrated to increase smoking cessation rates (Hughes, Stead & Lancaster, 2002) and decrease occurrence of withdrawal symptoms (Coleman, 2001). Its efficacy has also been reported in combination with both behavioural interventions (Hurt et al. 1997) and nicotine patches (Jorenby et al. 1999). Bupropion SR is currently prescribed to smokers who smoke more than 10-15 cigarettes per day and who are highly motivated to stop; the treatment has proven efficacy with this group, nearly doubling the success of smoking cessation (Coleman, 2001; Henningfield et al, 2000).

Bupropion SR is primarily a selective dopamine and noradrenaline re-uptake inhibitor, and it is thought to exert its cessation-enhancing effects by increasing dopaminergic activity (Settle, 1993; Ascher et al. 1995). The drug is equally effective in assisting cessation in smokers with or without a past history of depression, suggesting that its efficacy is not due to its antidepressant effect (Hughes et al. 1999a). Bupropion SR has been shown to mitigate increases in depression, difficulty concentrating and irritability following abstinence, and attenuate a decrease in positive affect (Shiffman et al. 2000). The drug is considered a useful option for smokers attempting to stop smoking for the first time, and in those who cannot tolerate NRT, those who prefer non-nicotine treatment, or those with whom NRT has failed (Hughes et al. 1999b).

Aside from bupropion, several other antidepressants have been investigated in terms of efficacy as a smoking cessation aid. These include nortryptaline, doxepin, fluoxetine and moclobemide and show limited if any success (Benowitz & Wilson Peng, 2000).

1.8.2.3 Clonidine, mecamylamine and other pharmacotherapies

Clonidine is an α2-noradrenergic agonist that suppresses sympathetic activity. It is an anti-hypertensive medication and has been used as a treatment of alcohol and opiate withdrawal (e.g. Gourlay & Benowitz, 1995; Gowing et al. 2002). Several early studies found that clonidine could also relieve craving for cigarettes and enhance smoking cessation (Ornish, Zisook & McAdams, 1988; Glassman et al. 1984). Prochazka et al. (1992) found that clonidine produced relief of withdrawal symptoms (anxiety and irritability) without finding enhanced quit rates. Gourlay & Benowitz (1995) report that both as pills and as a patch in low doses (0.2 - 0.4mg per day) clonidine increased smoking cessation in eight of nine trials. It has been recommended as a second-line therapy in US smoking cessation guidelines (Fiore, 2000).

Clonidine has more significant side effects (e.g. sedation, postural hypotension, dry mouth) and more dropouts due to side effects than NRT. The side effects clearly restrict its use and clinical effectiveness, and the drug's relevance to smoking cessation is clearly limited.

Mecamylamine is a nicotine antagonist originally used to decrease cholinergic activity, and thus reduce blood pressure (Clarke, 1991). It does not specifically bind at nAChRs but blocks the associated ion channel; this may be why, in humans, it blocks the effects of nicotine but does not precipitate withdrawal symptoms (Clark, 1991). Again however, side effects may limit the use of mecamylamine for smoking cessation. There are considerable gastro-intestinal effects, although these are less marked with lower doses.

Since smoking is often considered a means of reducing stress and anxiety (particularly by smokers) the potential efficacy of anti-anxiety drugs in smoking cessation has been investigated. Buspirone is associated with decreased nicotine withdrawal symptoms but efficacy has not been shown for smoking cessation (e.g. Covey et al. 2000). Naloxone and naltrexone, opioid antagonist drugs used extensively in treating alcohol and opiate addiction have been tested as smoking cessation aids. Results in terms of efficacy have been mixed (e.g. Covey et al. 2000).

Lobeline, a nicotine-like alkaloid has also been used as a form of smoking cessation therapy (Benowitz & Wilson Peng, 2000). Silver acetate, which interacts with cigarette smoke to produce an aversive metallic taste, has been tested as a smoking deterrent but is not shown to be efficacious (Hymowitz et al. 1993). Glucose has also been identified as a potentially cheap and simple smoking cessation aid with modest efficacy. Studies have shown that chewing glucose tablets can reduce the desire to smoke during periods of cessation (West, 2001).

1.9 Individual differences in smoking behaviour

Despite increasing interest and research in the field of cigarette smoking during the 1990s, the problem persists as to understanding why some people smoke and become nicotine dependent, others smoke as and when they feel like it with no discernible dependence, and others avoid smoking altogether.

Approximately only 40% of people who experiment with tobacco go on to smoke regularly. A popular theory as to why the other 60% escape addiction is that they have high innate sensitivity to nicotine and therefore experience the aversive effects on first

use more intensely, hence discouraging further experimentation (e.g. Silverstein et al. 1982). By contrast, those with lower initial sensitivity to nicotine will experience fewer or less intense aversive side effects, and as a consequence will be more likely to continue smoking.

Early self-administration is presumed to be maintained by social reinforcement, since the inception of smoking is usually an aversive experience. Following a certain "critical exposure" period, the social reinforcement is replaced by avoidance of nicotine withdrawal as the major motivator, signalling the development of dependence. Individual patterns will then emerge as each smoker's behavioural profile develops and stabilises, and these tend to be broadly categorised as "heavy" or "light" smokers. This rather arbitrary division is presented as purely dose-related, but implies that those who smoke more are highly nicotine dependent, have difficulty abstaining, are highly tolerant to nicotine and exhibit more withdrawal than light smokers on smoking cessation (Killen et al. 1988).

1.9.1 Tobacco chippers

Chippers (or non-addicted smokers) show no signs of withdrawal symptoms following overnight abstinence from smoking, and report being able to easily and regularly abstain from tobacco for periods of a few days or longer (Shiffman, 1989). Interestingly, it has been shown that chippers' nicotine absorption per cigarette and nicotine elimination rates were similar to those of heavy smokers (Shiffman et al. 1990; 1992; Brauer et al 1996). Chippers are less likely to smoke in order to relieve stress and to report an aversive response to their first ever cigarette, and also report having fewer smoking relatives (Shiffman, 1989; Kassel et al. 1994).

It is not clear what factors, if any, determine chipper status, and why this group is apparently protected from developing nicotine dependence, although there is evidence suggesting the group has a constitutionally reduced sensitivity to nicotine (Shiffman, 1991).

1.9.2 Models of nicotine tolerance

Chronic tolerance is believed to develop in proportion to extent of nicotine exposure (Gurling, Grant & Dangl, 1985). This *exposure model* of tolerance purports that whether an individual smokes or not is due to constitutional factors (based on initial sensitivity to nicotine), but that degree of dependence is governed by environmental variables (social "support for smoking" determining amount of nicotine exposure). Although this theory demonstrates considerable face validity, it overlooks a number of important factors that may shape smoking behaviour: e.g. differences in individual brain architecture and biochemistry, including different cholinergic psychopharmacology and arousal effects, nicotine metabolism factors, etc.

Recent critiques of the exposure model (e.g. Shiffman, 1991) have highlighted not only the theoretical shortcomings, but also the fact that the theory has achieved scant experimental support from the relevant human and animal research. Furthermore, it is practically and ethically extremely hard to determine the relationship between initial sensitivity to nicotine and tolerance. This is because appropriate research may involve administering the drug to nicotine-naïve adolescents. However, paradigms have been developed for studying individual differences in sensitivity to nicotine (Pomerleau et

al. 1993b; Pomerleau, 1995) that offer the prospect of future genetic studies on human subjective and physiological responses to nicotine.

Shiffman (1991) thus proceeded to propose a *sensitivity model* of tolerance, based on the theory that those individuals with a high initial sensitivity to nicotine not only derive greater aversive effects of the drug, but also greater reinforcement, and reinforcing effects (temporary improvements in affect and cognitive performance, amelioration of withdrawal symptoms). This is congruent with what is known about nicotine's psychopharmacological profile (see Section 1.7). In this theory, heavy smokers are hypothesised to be nicotine-sensitive individuals able to develop sufficient tolerance to the drug's aversive effects to sustain chronic use. When these individuals desist from smoking, they lose tolerance and suffer more intense withdrawal symptoms.

It is suggested that non-smokers and occasional smokers develop from that group with low nicotine sensitivity, as they experience less intense effects, hence less reinforcement, and do not persist with the drug (in the case of non-smokers), or use it fundamentally in social situations (in the case of occasional smokers). This model proposes that constitutional factors determine the degree of dependence possible, and in so doing shape the consequent pattern of smoking.

The sensitivity model is consistent with integrated models of tolerance (e.g. Poulos & Cappell, 1991). These integrated models of tolerance described it as a set of bio-behavioural adaptations consisting of both learned or associative factors (conditioned or behavioural tolerance) and non-associative factors (pharmacokinetic and

pharmacodynamic tolerance). This last group of factors addresses most of the problems with the exposure model, although arguably falls short of dealing with more complex neuropsychological variables.

It also fails to address the problem of "chippers" (see Section 1.8.1). These are regular smokers who are not tobacco dependent (i.e. they demonstrate few, if any, withdrawal symptoms upon interruption of their smoking pattern) (Shiffman, 1989). Although this group is arguably a "highly social" group of "social smokers", it is unlikely that tolerance alone can fully explain their ability to stave off the addiction trap.

1.9.3 Genetic influences on smoking

In contrast to the progress in understanding the genetics of alcoholism, the genetics for biological bases of smoking behaviour are still unclear. Nonetheless, several studies suggest genetic factors play a considerable role in determining which individuals who begin to smoke will become persistent long-term smokers. Genetic influences on nicotine dependence have been suggested by studies that used inbred rat and mouse strains (Marks et al. 1991). In recent years, human genomic research related to cigarette smoking has provided evidence for linkage of smoking behaviour to chromosomes 6, 9 and 14 (Bergen et al. 1999). Although the addictive qualities of nicotine contribute to chronic smoking, some individuals appear more susceptible than others. Some previously addicted smokers are able to quit while others are not; and some people may experiment with cigarettes without becoming regular smokers.

Heath & Madden's (1995) review presents results from national twin surveys in Scandinavia and Australia from the 1960s to the early 1980s. They consistently report

that heritable factors explain variance affecting the probability of becoming a regular smoker ('initiation') and the risk that those who become regular smokers will become long-term persistent users ('persistence'). Increasing our understanding of genetic and environmental contributions to smoking initiation and persistence may enhance our ability to identify and prevent smoking in those most predisposed to becoming regular smokers, and improve cessation for persistent smokers. Linkage data indicate that the effects of genes on smoking behaviour are weak, or that gene alleles that influence smoking behaviour occur in only a small proportion of families.

Twin studies support an important family environmental influence on initiation of smoking, and suggest an additional genetic influence (Boomsma et al. 1994; Heath & Madden, 1995). Findings of genetic influence on smoking persistence have been variable. Heath (1990) failed to find any evidence of genetic influences on persistence that were independent of the determinants of smoking initiation. However, data from a larger cohort found evidence for an important genetic influence on risk of smoking persistence in regular smokers that was independent of genetic influences on onset of smoking (Heath & Martin, 1993). Re-analysis of early twin studies in Scandinavia found evidence for substantial genetic influences on persistence that were unrelated to effects on onset (Medlund et al. 1977; Kaprio et al. 1978). A much weaker genetic effect was found in men than in women in the former study, although no interaction with gender was found in the latter (Heath et al. 1995; Heath & Madden, 1995).

True et al. (1997) analysed twin data using a model allowing for both genetic and shared environmental effects on smoking initiation, which demonstrated accounts of 50% and 30% of variance in risk respectively. However, this model solely allowed for

genetic effects on persistence in smoking among regular smokers, and this accounted for 70% of variance in risk. Therefore, findings to date suggest that there is stronger support for a genetic basis of smoking *persistence* than smoking *initiation*.

1.9.3.1 Smoking behaviour and genetic differences in dopaminergic neurobiology

Taking into consideration evidence suggesting the importance of dopaminergic systems to addictive behaviour (Section 1.7.1), genes regulating its activity are likely to be involved in nicotine dependence and smoking behaviour. Among the five dopamine receptor subtypes investigated so far, the D1, D2 and D3 subtypes are prevalent in the mesolimbic system and are most clearly implicated in the reinforcing effects of drugs (Clarke, 1998).

There are few studies examining DRD1 polymorphisms in relation to smoking behaviour. Comings et al. (1997) reported an association between homozygosity for either allele of a *Dde*I polymorphism (–A/G) and smoking, although the functional significance of this polymorphism is yet to be clarified. Duggirala et al. (1999) reported linkage of smoking behaviour to marker D5S1354 on chromosome 5q: this marker is located close to the genes for the D1 dopamine receptor (DRD1).

The *Taq*I A* polymorphism is the most extensively studied of the many DRD2 gene polymorphisms. Although thought not to be functional, *Taq*I A1 allele is associated with reduced DRD2 availability in the striatum (Jonsson et al. 1999). Significant inverse associations have been reported between the prevalence of *Taq*I A* allele and the age of smoking onset and to the maximum period of time for which smokers were able to abstain from smoking (Comings et al. 1996; Noble et al. 1994). Associations

have also been reported between smoking and DRD2 gene polymorphisms in smoking incidence (Spitz et al. 1998; Yoshida et al. 2001), although these results are contested (Bierut et al. 2000).

High densities of DRD3 are present in the nucleus accumbens (Arinami et al. 2000). Various polymorphisms have been identified, including the Ser9Gly polymorphism (Lannfelt et al. 1992). Associations have been reported between the homozygosity for the Ser9Gly polymorphism and both cocaine dependence (Comings et al. 1999) and opiate dependence (Duaux et al. 1998). Despite the variety of DRD3 polymorphisms, their association with smoking behaviour has not been examined.

1.9.3.2 Smoking behaviour and genetic differences in personality via dopaminergic neurobiology

Another route by which the dopamine system and smoking behaviour may be linked is via inherited personality traits, or genotypes encoding likely behavioural characteristics resistant to change or environmental adjustment. Personality is the characteristic manner or style of an individual's behaviour as opposed to goals towards which it is directed (motivation), or the machinery of its execution (cognitive and motor skills). Gray (1973) argues that personality traits reflect motivational systems that evolved to increase adaptation to classes of stimuli associated with positive and negative reinforcement. Individual differences in personality thereby reflect variation in the sensitivity to such stimuli, and overall personality represents the relative strength of sensitivities to various stimulus classes. For example, impulsive people can be described as more sensitive to reward than to punishment, approaching rewarding situations even when punishers make restraint more

appropriate. Sensitivity ultimately means reactivity of the neurobiology associated with a motivational system (Depue & Collins, 1999).

The majority of genetic research on personality involves self-report questionnaires. Responses to such questions are remarkably stable, even over several decades (Costa & McCrae, 1997). Questionnaires utilised include: the Revised NEO Personality Inventory (NEO-PI-R) (McCrae & Costa, 1997), Eysenck's Personality Inventory (EPI) (Eysenck & Eysenck, 1964), Cattell's 16 PF (Cattell, 1947), Cloninger's Temperament & Character Index (TCI) (formerly Tridimensional Personality Questionnaire, or TPQ) (Cloninger et al. 1993). All these self-report questionnaires reliably measure many of the same personality factors, especially the more robust categories of Novelty Seeking (extraversion, conscientiousness, sensation-seeking, psychoticism) and Harm Avoidance (neuroticism, anxiety-related traits).

Cloninger's personality questionnaires were developed as tools to study the genetics of personality. The questionnaires draw on human and animal work to suggest that behaviour is mediated by certain neurotransmitters, which underlie three basic and largely heritable dimensions, called "Novelty Seeking", "Harm Avoidance" and "Reward Dependence". Novelty Seeking taps aspects of impulsiveness, curiosity (or exploratory behaviour in animals) and disorderliness.

Smokers report higher Novelty Seeking scores than non-smokers (Pomerleau et al. 1992). There are several sub-scales of Cloninger's Novelty Seeking trait. Of these, Impulsivity (impulsiveness) perhaps represents the strongest link to smoking behaviour. A high level of impulsivity has been equated with preferences for

immediate gratification, risky activities, novel sensations, and easier routes to self-gratification, as well as an inability to persist at a task and shorter reaction times (e.g. McCown et al. 1993). People with high levels of impulsivity are thought to be more likely to experiment with psychoactive drugs and possibly become regular users (Johnson et al. 1993; Logue, 1995). A study examining various scores on the Sensation-Seeking Scale (Zuckerman, 1971) found that smokers scored higher than non-smokers (Carton et al. 1994). There are many other studies reporting higher levels of impulsivity in smokers than in non-smokers (e.g. Williams, 1973; Golding et al. 1983; Zuckerman et al. 1990; Jenks, 1992; Mitchell, 1999).

Novelty Seeking, the increased tendency to respond to novel and promising situations, is principally served by the mesolimbic dopamine system. Rewarding activities, including certain drugs such as nicotine, increase dopamine release or inhibit its re-uptake in the mesolimbic system (Schultz, 1997). Because of its critical role in the elicitation of euphoria in humans and exploratory approach behaviour in other animals (Cloninger, 1987), dopamine has been hypothesised as the main neuromodulator of Novelty Seeking.

Associations have recently been reported between a specific genetic polymorphism and a specific personality trait. Ebstein et al. (1996) studied Novelty Seeking in normal volunteers and found an association with the 7-repeat allele of the DRD4 exonic polymorphism. Similarly, Benjamin et al. (1996) reported population and familial associations between DRD4 gene polymorphisms and measures of Novelty Seeking. Ono et al. (1997) replicated this result in Japanese female students. These findings have been further replicated by some studies (Kuhn et al. 1999; Noble et al.

1999) and contradicted by others (Bau et al. 1999; Gelernter et al. 1997; Jonsson et al. 1998; Sullivan et al. 1998).

These initial studies examined the role of the exon III 48-bp repeat dopamine D4 receptor polymorphism in personality. This gene has a highly polymorphic region in the third cytoplasmic loop that varies between 2 and 10 repeats in most populations and changes the length of the receptor protein (Lichter et al. 1993). Variants in the polymorphism are usually written "D4.*x*", where *x* represents the number of repeats. The dopamine D4.2, D4.4 and D4.7 receptor alleles occur the most frequently, but there is considerable variation in the distribution of alleles depending on ethnicity (Chang et al. 1996; Lichter et al. 1993).

There is some evidence that the long (L) and short (S) alleles of this protein have moderate functional significance with L alleles demonstrating relatively lower affinity for dopamine (Asghari et al. 1994), although a more recent study presents contradictory evidence (Kazmi et al. 2000). Both the Benjamin et al. (1996) and Ebstein et al. (1996) studies suggested an association between Novelty Seeking and the L alleles of DRD4.

An association between smoking behaviour and the DRD4 L allele has been reported for an African-American population (Shields et al. 1998). This study found that after smoking cessation counselling, none of the subjects with an L allele were abstinent at 2 months compared with 35% of the subjects who were homozygous for the S allele. This association, however, was not reported in Caucasian subjects. This study also reports that subjects who had at least one L allele had higher risk of smoking, shorter

time to first cigarette in the morning and earlier age at smoking initiation. An association was also found between this polymorphism and opioid-dependence (Kotler et al. 1997; Li et al. 1997), raising the possibility that D4 receptor genetics might have some generic influence on addiction.

As stated, there is strong evidence of an association between the L allele and the Novelty Seeking personality trait (e.g. Ebstein et al. 1996; Benjamin et al. 1996). Since smokers showed higher Novelty Seeking rates than the general population (Pomerleau et al. 1992; Zuckerman et al. 1990), it is likely that the L allele is associated with smoking, concordant with Shields et al.'s (1998) reported findings with the African-American smokers.

1.10 Aims of the current research

The aims were to define addicted versus non-addicted smokers, and explore the role withdrawal may contribute to these differences by studying (a) mood and cognitive performance, (b) genes affecting dopaminergic neurobiology, (c) psychosocial variables, and (d) withdrawal symptomatology. Finally, the (e) withdrawal-mediated involvement of noradrenergic systems in tobacco withdrawal was investigated.

Using questionnaire data it was possible to derive a Nicotine Addiction Index, a composite score quantifying levels of nicotine dependence. This was subsequently investigated to reveal two distinct groups, labelled addicted and non-addicted smokers.

Differences in changes in mood and cognitive performance following nicotine withdrawal and reinstatement between addicted smokers and non-addicted smokers were examined. There is a large body of evidence supporting the existence of a sub-group of regular or habitual smokers dubbed "chippers" (Section 1.9.1), who seem able to tolerate prolonged periods of abstinence with no overt or reported withdrawal symptoms (e.g. Shiffman, 1989; 1991). One of the main aims of this PhD research was to elucidate why these individuals are able to regularly self-administer nicotine, a highly addictive drug, without developing dependence as in the majority of smokers consuming comparable levels of the substance. Some work has been done looking at possible relationships between psychosocial or personality variables and chipper status, but with weak or inconclusive results (Kassel et al. 1994).

Predictions

It is hypothesised that withdrawing nicotine would cause a decline in mood and deterioration in cognitive performance in all smokers, but particularly the addicted smokers. Non-addicted smokers, effectively smokers demonstrating low tolerance and citing fewer addictive motivations for smoking) were not expected to show uniform impairments or significant effects of withdrawal. The addicted smoker group was expected to report greater withdrawal symptoms than other groups. It was predicted that there would be differences in responses to nicotine reinstatement between the two "types" of smoker. The addicted smokers were expected to demonstrate a considerable improvement in mood and cognitive performance following nicotine reinstatement, whereas the non-addicted smokers may have displayed some improvement, but not so marked.

DNA analysis was performed on experimental subjects. In recent years there has been some evidence that genetic predisposition to nicotine addiction or "addictiveness" may exist. In particular, polymorphic genes affecting dopaminergic function have been associated with variations in addictive behaviour or potential. Dopamine receptor sub-types D2, D3 and D4 were examined. Furthermore, DRD4 is a dopamine receptor believed to be associated with novelty-seeking behaviour. There is strong evidence that individuals' having a D4 L-allele genotype score consistently higher on Cloninger's Novelty Seeking trait than those with the other sub-type. It was predicted that addicted and non-addicted smokers would have consistently different dopamine receptor genotypes, with the former group possessing the L-allele. Smoking behaviour could be related to novelty-seeking, or related personality characteristics such as impulsivity. It was also hypothesised that addicted smokers will have higher Novelty Seeking scores than the other groups.

Smoking behaviour and its relationship with personality and psychosocial variables per se was also examined. It is pertinent that there may be personality or social variables that can predict smoking behaviour, and these data may illuminate possible character or environmental differences between non-addicted and addicted smokers. Although Kassel et al. (1994) found only weak associations between smoker status and personality and psychosocial variables, their methodology and findings justify expansion of their research. It is possible that their modest findings were as a result of failure to measure enough variables, or by not examining interactions, or because of their subject sampling protocol. There are a number of previous studies suggesting that smoking motivation factors may predict severity of nicotine withdrawal symptoms, and thus level of dependence or addiction (e.g. West & Russell, 1985).

All the above studies utilised a control group of non-smokers, whether questionnaire, performance or DNA. It was hypothesised that there would be greater concordance between the non-smokers and non-addicted smokers on inter-session changes in most measures, as their psychological and psychopharmacological systems are arguably more similar (lower nicotine tolerance, less novelty-seeking personality characteristics, etc.).

Finally, noradrenergic involvement in tobacco withdrawal was investigated. The impact of lofexidine was compared with NRT on the tobacco withdrawal syndrome in a repeated measures study. Addicted smokers were assessed in terms of mood, cognitive performance, withdrawal symptoms and urges to smoke following withdrawal on four separate occasions. Lofexidine was expected to alleviate impairments and symptoms associated with tobacco withdrawal as effectively as NRT and better than placebo.

Chapter 2 - Definition of addicted and non-addicted smokers

2.1 Introduction

Identifying what proportion of smokers is dependent is a complex question. Tobacco dependence can best be conceptualised as existing on a continuum rather than as a dichotomous variable (dependent vs. non-dependent), although a functional categoric division is useful in, for example, directing treatment. Difficulty abstaining and a perception of compulsion to smoke are central to the definition of nicotine dependence: this epitomises the lack of control viewed as fundamental to all dependence. There is evidence that degree of dependence, when defined as difficulty in abstaining, is closely related to frequency of smoking (Etter et al. 1999).

A UK national statistics survey by Walker et al. (1998) found that 58% of current smokers state they would find it fairly or very difficult to abstain from smoking for only one day. Furthermore, Walker et al. (1998) state that those smoking 20 or more cigarettes a day are more likely to say it would be difficult than those smoking less than 10 a day (83% vs. 23%). Evaluating the proportion of non-dependent smokers is clearly related to definitions of both "dependence" and "a smoker".

The term "chippers" was first used by Zinberg & Jacobsen (1976) to refer to opiate users who were capable of limiting and controlling their use of opiates as opposed to the common pattern of escalating and compulsive opiate use which many had come to associate with heroin users. They highlight what has now become a reliable axiom: that drugs which have strong dependence-producing qualities in many people do not necessarily produce dependence in all users (e.g. Powell, 1973). Following these early

studies examining non-dependent heroin users, it has been recognised that not all tobacco smokers progress to become highly dependent chain smokers.

Shiffman was one of the first to systematically study the phenomenon of non-dependent smokers, and he also used the term "chippers" (Shiffman 1989). There is consensus in the literature that adults who consistently smoke five or fewer cigarettes per day, but who smoke at least four days a week over a long period (e.g. more than a year) are non-dependent. Walker et al. (1998) state that up to 20% of UK smokers report smoking fewer than five cigarettes a day, but it is unclear what proportion of these people are in a transitional phase of increasing or decreasing consumption. Many smokers preparing to quit decrease consumption prior to stopping, and this subgroup could confound the reliability of the statistics (e.g. Owen et al. 1995). It has been estimated that only about 5% of smokers are able to smoke without becoming addicted (Shiffman, 1991).

Initial studies of "chippers" compared them with heavy smokers (20-40 cigarettes per day). Light smokers (<20 per day) reported no signs of nicotine withdrawal after overnight abstinence and, in contrast to heavy smokers, also reported that they could regularly and easily abstain from tobacco for a period of a few days or longer (Shiffman, 1989). These findings confirmed that chippers were at the low end of the dependence continuum. However, it was also found that nicotine absorption per cigarette in the chippers and nicotine elimination rates were similar to those of heavy smokers (Shiffman, 1992). Chippers were less likely to smoke to relieve stress, less likely to report an aversive response to their first ever cigarette, and reported having fewer relatives who smoked (Shiffman, 1989). Hajek, West & Wilson (1995)

compared very light smokers (consistently less than 6 cigarettes a day) with regular smokers in a cohort of women followed up for a year. This study found that very light smokers had higher educational attainment, more non-smoking relatives, but also more very light smokers among their relatives, lower neuroticism scores, and were less likely to state that they smoked in order to help them cope.

Pomerleau et al. (1993b) suggest that vulnerability to nicotine dependence may be related to genetically based high initial sensitivity to nicotine; others present data purporting that genetic influences on smoking behaviour are more related to persistence (Heath & Madden, 1995). People who become highly dependent smokers have been found to have more pleasurable situations at their initial exposure to tobacco (Pomerleau, Pomerleau & Namenek, 1998). This may be perceived as contradicting Shiffman's (1989) findings that regular smokers recalled more unpleasant reactions to their first cigarette than chippers. Furthermore, research indicates that initial dizziness predicted increased likelihood of rapidly progressing to further smoking in children (Hirschman, Leventhal & Glynn, 1984).

Shiffman (1989) found that chippers reported motivations to smoke were significantly different to those of regular smokers. Chippers scored considerably lower on the Addictive smoking factor of Horn's (Ikard et al. 1969) Reasons for Smoking scale, suggesting that internal cues characterising dependence were not responsible for initiating smoking behaviour in this subgroup. This scale is an early example of a questionnaire attempting to characterise the heterogenenity of smokers' motivations for smoking. This questionnaire presented a cluster of items measuring "addictive smoking", and yielded a factor recognisable as such. A similar attempt to classify

smokers by a factorial structure of motives was performed later (Russell et al. 1974), and again a recognisable "addiction" factor was elicited from their expanded questionnaire. Russell et al. (1974) proposed their factor structure as a tool for classifying smokers on a singular dimension of "nicotine addiction", rather than proposing a truly multi-factorial aetiology.

Chronic nicotine tolerance is generally believed to be central to tobacco dependence (e.g. Pomerleau et al. 1993a). It has been shown to be present in both current smokers and ex-smokers, and a questionnaire has been devised and validated to quickly ascertain levels of physical dependence (Fagerström, 1978). Data from studies investigating tolerance suggest that smoking immediately on waking may be the best indicator of dependence (Fagerström, 1978; Kozlowski, 1981). Both chippers and their relatives who smoke have longer latency to smoke after waking, suggesting lower levels of tolerance relative to regular or dependent smokers (Shiffman, 1989; Shiffman et al. 1995) and a potential genetic involvement (Gurling et al, 1985). Chippers clearly smoke fewer cigarettes than dependent smokers (Shiffman, 1989) although whether this represents lower biological "need" for nicotine or another reason is unclear.

Smokers have been shown to have less negative beliefs about smoking than non-smokers (Haddad & Malak, 2002; Panter & Reeve, 2002). Whether these reported attitudes are authentic or the outcome of cognitive dissonance (whereby beliefs are readjusted due to a conflict with an individual's behaviour) is a contentious issue. Chippers have been shown to have more positive smoking beliefs than non-smokers, but less than heavy smokers (Presson, Chassin & Sherman, 2002).

The current research included the development of a brief questionnaire measuring smokers' beliefs regarding 10 putative aspects of smoking (positive and negative) called the Smoking Beliefs Inventory. This was generated by "brainstorming" focus groups of smokers.

The aim of this research was to accumulate a database of smokers and gain a comprehensive picture of the nature of their habit, and to develop an "Addiction Index" score quantifying levels of tobacco dependence. This composite score would comprise of summed, appropriately weighted numbers computed from reported levels of dependent motivations for smoking and nicotine tolerance. Using this Addiction Index, we aimed to investigate differences between dependent and non-dependent smokers. To this end, a questionnaire battery was compiled comprising several previously validated questionnaires about motivation for smoking, demographic data and questions about smoking behaviours, tobacco tolerance and smoking beliefs.

The following hypotheses were investigated:

I. that by generating an Addiction Index score, using tolerance and motivational self-report data to quantify levels of dependence, addicted and non-addicted subgroups of smokers can be identified and characterised.

II. that subgroup status (addicted / non-addicted) would be associated with self-reported addiction to smoking, gender, being daytime rather than evening smoker, partner's smoking status, reported increased smoking when

consuming tea or coffee, increased smoking when consuming alcohol and parents knowledge of smoking behaviour.

III. that greater levels of dependence would be positively correlated with reported number of cigarettes smoked, number of quit attempts and number of months being a smoker.

IV. that greater levels of dependence would be negatively correlated with age smoking behaviour commenced and latency to first cigarette of the day.

V. that greater levels of dependence would be positively correlated with agreement with positive belief statements about smoking.

2.2 Method

2.2.1 Design

This was a cross-sectional self-report questionnaire-based study of smokers, detailing profiles of smoking-related motivations, behaviours and beliefs. The Smoking Questionnaire Battery (SQB) was a composite questionnaire constituting a short demographic section, questions regarding subjects' individual smoking behaviours and two validated questionnaires regarding motivations for smoking (Smoking Motivation Questionnaire – SMQ and Reasons for Smoking - RFS). Also included were questionnaires measuring estimated nicotine tolerance (Fagerstrom Tolerance Questionnaire, FTQ), and looking at beliefs about the mental and physical effects of smoking (Smoking Beliefs Inventory, SBI).

Also included in this booklet were questions regarding the subjects' willingness to participate in further experimental studies pertaining to smoking. Subjects were also asked to complete a psychosocial questionnaire booklet. This featured several extensive questionnaires regarding health-related behaviours, social support, perceived stress, psychological disturbance, etc. and is discussed in Chapter 5.

2.2.2 Subjects

Subjects (n=109) were recruited by means of posters around the University of Bristol campus advertising for smokers to come and complete a questionnaire battery for which they would be paid £5. They were also invited to take part in the mood & cognitive performance study (described in the Chapter 3). Respondents were primarily undergraduates and postgraduates at the University of Bristol, although members of the general public were also recruited via word of mouth. Subjects ages ranged from 16 to 54 (mean=23.3, SD=5.9): 49 male, 57 female. Three subjects chose not to state their gender.

2.2.3 Questionnaires

Reasons For Smoking (RFS) Questionnaire/Horn-Waingrow scale (Ikard, Green & Horn, 1969). This was one of the first questionnaires developed to ask people for reasons for their smoking. It is a 23-item self-report questionnaire, requiring a judgement by the respondent concerning the extent to which ("always", "frequently", "occasionally", "seldom", "never") the behaviour was typical of their own. The response was registered for each item by circling the appropriate number on a 5-point Likert scale (1 to 5). See Appendix I.

Smoking Motivation Questionnaire (SMQ) (Russell, Peto & Patel, 1974).

A 34-item self-completion questionnaire based on smoking motive themes drawn from previous published work by McKennell (1970) and Ikard et al. (1969). Subjects were asked to respond in terms of a four-point scale which was scored as follows: "not at all"=0, "a little"=1, "quite a bit"=2, "very much so"=3. See Appendix II.

Fagerstrom Tolerance Questionnaire (FTQ) (Fagerström, 1978).

This 8-item questionnaire was intended to measure physical dependence to nicotine. Subjects had free response to items 1, 2, 5 & 6; Item 3 was responded to by circling "always", "sometimes" or "never", and the remainder were responded to by circling "Yes", "No" or "Depends". See Appendix III.

Smoking Beliefs Inventory (SBI) (Hayward, unpublished)

This 10-item questionnaire was generated in order to examine beliefs about smoking. It was generated from points made during brainstorming sessions of an informal focus group and presents several ideas about smoking that have been experimentally investigated. It makes positive and negative statements about putative general effects of smoking and asks subjects to rate how much they agree with the statements on a Likert-scale ("strongly disagree"=0, "slightly disagree"=1, "undecided"=2, "slightly agree"=3, and "strongly agree"=4). See Appendix IV.

2.2.4 Procedure

Smokers completed the Smoking Questionnaire Battery (SQB) in their own time, either at home or work, or in the Health Psychology Research Unit, University of Bristol.

2.3 Analyses

Data were entered using Microsoft Access and analysed with SPSS Version 9.0 and BMDP. Principal components factor analysis was performed on the motivation questionnaires and analysis of variance was performed to verify the difference between the addicted and non-addicted subgroups. Pearson's Chi-square was used to test associations between subgroup status and variables with categoric data. Spearman's Rho was used to analyse correlation between Addiction Index scores and variables with continuous data.

2.4 Results

Results were based on data acquired from 103 subjects who had successfully completed the Smoking Questionnaire battery (six subjects were omitted from the analyses due to incomplete questionnaires).

2.4.1 Calculating the Addiction Index and generating subgroups (addicted vs. non-addicted smokers)

Individual factor analyses were performed on the questionnaires examining reasons for smoking, and factor scores computed for each subject. The Smoking Motivation Questionnaire (SMQ) and Reasons For Smoking (RFS) scale each yielded factor structures that were very similar to those found in the original paper. This included "addictive smoking" or "addiction" factors comparable to previous findings, and the factor scores of these were retained for use.

Factor analysis of the RFS produced a five-factor structure. Factor 1 explained approximately 36% of the variance (Eigenvalue 8.22) and was labelled "Addiction"

(items relating to the compulsive or habitual aspects of smoking). The questionnaire items loading on the "Addiction" factor derived for the RFS by principal components analysis with varimax rotation were (factor loadings): 8 (0.87), 18 (0.75), 22 (0.73), 13 (0.71), 10 (0.71), 20 (0.66), 5 (0.65), 15 (0.62), 3 (0.55) and 4 (0.54) (Table 2.1). The sample frequency of RFS "Addiction" factor scores was negatively skewed and ranged from 9 to 40 with a mean of 20.38 (SD 7.91) (Figure 2.1). Factor 2 explained approximately 11% of the variance (Eigenvalue 4.29) and was labelled "Negative affect reduction" (items pertaining to smoking in order to mitigate negative emotions). Factor 3 explained approximately 8% of the variance (Eigenvalue 1.84) and was labelled "Stimulation" (items pertaining to smoking in order to increase arousal or concentration). Factor 4 explained approximately 6% of the variance (Eigenvalue 1.40) and was labelled "Pleasurable Relaxation" (items pertaining to smoking for its own sake or while relaxing). Factor 5 explained approximately 5% of the variance (Eigenvalue 1.26) and was labelled "Sensori-motor" (items loading on this factor pertained to sensory aspects of smoking).

Factor analysis of the SMQ produced a ten-factor structure. Factor 1 explained approximately 20% of the variance (Eigenvalue 6.27) and was labelled "Psychosocial" (items pertaining to the social aspects of smoking). Factor 2 explained approximately 11% of the variance (Eigenvalue 4.29) and was labelled "Stimulation" (items pertaining to smoking in order to increase arousal or concentration). Factor 3 explained approximately 8% of the variance (Eigenvalue 2.83) and was labelled "Addiction" (items relating to the compulsive or habitual aspects of smoking). The questionnaire items loading on the "Addiction" factor derived for the SMQ by principal components analysis with varimax rotation were (factor loadings): 10 (0.81),

9 (0.74), 17 (0.66), and 31 (0.63) (Table 2.2). The sample frequency of SMQ "Addiction" factor scores was also negatively skewed and ranged from 0 to 13 with a mean of 4.26 (SD 2.81) (Figure 2.2).

Factor 4 explained approximately 5% of the variance and was labelled "Sedative" (items loading on this factor pertained to smoking while relaxing). Factor 5 also explained approximately 5% of the variance and was labelled "Sensori-motor" (items loading on this factor pertained to sensory aspects of smoking). Factor 6 explained approximately 4% of the variance and was labelled "Automatic" (items loading on this factor pertained to sub-conscious smoking behaviours). The remaining factors were labelled "Postprandial", "Alcohol-associated", "Sharing" and "Oral"; these factors mainly had single items loading on them, and when combined accounted for 10% of the variance.

Totalled scores on the Fagerstrom Tolerance Questionnaire ranged from 1 to 9, with a mean of 3.9 (SD 1.98) (Figure 2.3). The FTQ is a powerful tool for identifying and diagnosing nicotine dependence, and Spearman's Rho demonstrated FTQ was significantly positively correlated with RFS "Addiction" factor ($r=0.65$, $p<.001$, 2-tailed) and with SMQ "Addiction" factor ($r=0.52$, $p<.001$, 2-tailed).

The scores from the FTQ, "Addiction" factor scores from RFS and SMQ and the binary selection response to "would you say are you addicted to smoking? (Yes/No)" (self-reported addiction status) were considered important in the initial generation of a score quantifying a multi-source level of tobacco-dependence. Using and combining the data acquired using these questionnaire tools it was possible to formulate an

"addiction score" for each respondent. Scores from each component questionnaire were divided by their standard deviations in order to appropriately weight the items, and they were then summated to create a "composite addiction score". In this way it was possible to profile the sample in terms of how tobacco-dependent they were.

- ADDICTION INDEX (composite addiction score) = *addx*
- Reasons For Smoking "Addiction" Factor Score = *RFSscx*
- Smoking Motivation Questionnaire "Addiction" Factor Score = *SMQscx*
- Fagerstrom Tolerance Questionnaire score = *FTQx*
- Self-reported addiction status = *SRx*

Thus, each subject's Addiction Index was calculated by the following:

$$addx = \frac{RFSscx}{SD\{RFSscx\}} + \frac{SMQscx}{SD\{SMQscx\}} + \frac{FTQx}{SD\{FTQx\}} + \frac{SRx}{SD\{SRx\}}$$

This initial Addiction Index score ranged from 1.5 to 13.7 with a mean (SD) of 7.39 (3.08). The resultant score distribution was normal (Gaussian), although negatively skewed (Figure 2.4). A median split was chosen to divide the addicted and non-addicted smoker groups.

Many of the analyses performed when the groups were subdivided in this way indicated trends predicted by the experimental hypotheses, but with few significant results. Although there were several possible explanations for this (including the truth of the null hypotheses), it was likely that non-significant results were obtained due to the way subjects were allocated into their groups.

The model generating the Addiction Index was subsequently refined. Including subjects' own assessments of their addiction status (*SRx*) as an attempt to quantify nicotine addiction may not have been appropriate. It is likely that there will normally be considerable correlation between addicts' objective and subjective data regarding their status. However, not all addicts claim to be addicted, and likewise some non-dependent users will claim to be addicted to explain their behaviour. Although weighted, the *SRx / SD(SRx)* represented a considerable portion of the *addx* total. This was possibly responsible for non-addicts seeking to justify their smoking behaviour by defining themselves as tobacco-dependent, i.e. addicted. It was possibly also responsible for putting addicted smokers in denial of their addicted status in the non-addicted group. It was therefore decided to review the equation calculating Addiction Index without the subjective "are you addicted to smoking?" data, thus:

$$addx = \frac{RFSscx}{SD\{RFSscx\}} + \frac{SMQscx}{SD\{SMQscx\}} + \frac{FTQx}{SD\{FTQx\}}$$

The new Addiction Index score ranged from 1.5 to 11.4 with a mean (SD) of 5.76 (2.48). This changed the histogram profile of the sample. Although still negatively skewed, it showed a possible emergence of a bi-modal distribution (Figure 2.5). This distribution, because of the skewness, did not fail a test of normality and therefore cannot be formally labelled bi-modal.

It was decided to define addicted and non-addicted groups by assuming Figure 2.5 represented a true bi-modal distribution, with those subjects possessing an Addiction Index score of 8.00 or greater labelled "addicted". This yielded groups of 20 "addicted" smokers and 83 "non-addicted" smokers from the 103 participants. To demonstrate meaningful dichotomy at the Addiction Index cutpoint of 8.0, the means

of the two groups were compared using a one-way analysis of variance and found to be significantly different ($F\{1,99\}=197.62$, $p<.001$).

2.4.2 Demographic, behavioural and smoking belief differences between addicted and non-addicted smokers

Following the factor analysis and generation of the Addiction Index scores, correlations and associations were performed to examine the relationships between the variables in the SQB (demographic, behavioural and beliefs) and the subgroup status or Addiction Index scores. Tables 2.3, 2.4 and 2.5 present either means and standard deviations or relative percentages for addicted and non-addicted smokers for variables analysed in this section.

2.4.2.1 Subgroup status (addicted vs. non-addicted) and association with demographic and behavioural variables

Pearson Chi-square demonstrated that several SQB variables were associated with smoking group status. Addicted smoker status was associated with being male ($\chi^2=4.74$, $p<.05$). Self-reported addiction to smoking was associated with addicted smoker group status ($\chi^2=8.65$, $p<.01$) (Figure 2.6). Parental awareness of participants smoking behaviour was associated with addicted smoker status ($\chi^2=6.34$, $p<.05$). Addicted smoker status was also associated with reported increased smoking when consuming tea or coffee ($\chi^2=10.24$, $p<.001$) (Figure 2.7), but not with reported increased smoking when consuming alcohol.

There was no significant association between smoker group status and mostly smoking in the daytime. Having a partner who smoked was not significantly associated with smoker group status.

2.4.2.2 Correlation between demographic, behavioural and smoking beliefs and Addiction Index scores

Spearman's Rho demonstrated that Addiction Index scores were positively correlated with number of cigarettes smoked each day ($r=0.69$, $p<.001$, 1-tailed), and that Addiction Index scores were positively correlated with number of months subjects had smoked ($r=0.28$, $p<.01$, 1-tailed). No correlation was found between Addiction Index score and number of attempts to quit.

Spearman's Rho also demonstrated that Addiction Index scores were negatively correlated with latency to first cigarette smoked after waking ($r=-0.65$, $p<.001$, 1-tailed) (Figure 2.8). No correlation was found between Addiction Index score and age smoking behaviour commenced.

Addiction Index scores were positively correlated with the following positive smoking beliefs as tested by Spearman's Rho: "smoking can help people relax" ($r=0.38$, $p<.001$, 1-tailed); "smoking can help people when they feel nervous or embarrassed" ($r=0.17$, $p<.05$, 1-tailed); "smoking improves concentration" ($r=31$, $p<.001$, 1-tailed); "smoking is pleasurable" ($r=0.31$, $p<.001$).

It should be noted that some of these significant associations and correlations might be explained by the fact that similar or related items included in the questions that contributed to the formulation of the Addiction Index score.

2.5 Discussion

These results suggest that the Smoking Questionnaire Battery administered was an effective tool for identifying levels of tobacco dependence. "Addiction" factor components derived from factor analyses of the RFS and SMQ were consistent with those indicated in the original reports. Using a composite model based on the data they provided and FTQ scores it was possible to establish an "Addiction Index" score representing an appropriate quantification of level of nicotine dependence. By profiling this sample's Addiction Index frequency data two groups of smokers were identified, labelled "addicted smokers" and "non-addicted smokers". "Addicted smoker" status was associated with being male, self-reporting addiction to smoking, parents knowledge that subject was a smoker, increased smoking when drinking tea or coffee.

The Addiction Index score was positively correlated with number of cigarettes smoked per day, total number of months subject had been a smoker; and negatively correlated with latency to first cigarette after waking. The Addiction Index score was also positively correlated with believing that smoking can help people relax, can help people when they feel nervous or embarrassed, improves concentration and is pleasurable. The subgroups of addicted and non-addicted smokers were shown to possess good face validity and were functional in later chapters. Significant

differences between the subgroups' smoking behaviours, motivations and beliefs were demonstrated.

The questions in the Smoking Questionnaire Battery are comprehensive in terms of asking people why they smoke, although some of the questionnaires used may be in need of updating. The principal components analysis performed on the RFS produced a five-factor structure comparable with the original Ikard et al. (1969) report. The current structure consisted of factor labelled "Addiction", "Negative affect reduction", "Stimulation", "Pleasurable relaxation" and "Sensori-motor". This factor structure was very similar to Ikard et al. (1969). The "Addiction" factor of the current study comprised the same questionnaire items in the original report, however this current analysis amalgamated the "Addictive" and "Habitual" factors of the original. In essence this does not present a theoretical difficulty, as it can be argued that the "Habitual" items effectively represent the behavioural manifestation of the addiction.

The "Addiction" factor of the current RFS analysis also included an item ("When I am trying to solve a problem, I light up a cigarette") in Ikard et al.'s (1969) "Reduction of negative affect" factor. This may have been an artefact, or perhaps an indication that smoking in order to alleviate stress may be correlated with nicotine dependence. It might be argued that this item is more relevant to stimulation smoking, but loaded very weakly on the "Stimulation" factor in the original report (-0.09), and only slightly more on the "Stimulation" factor in the current structure (0.26). It can be seen that the original and current factor structures are highly consistent, albeit that two factors have been combined in the present analysis. It was decided that factor scores from the RFS "Addiction" factor would be a valuable and effective tool in quantifying

nicotine dependence, as they cumulatively rate subjects' addiction- or dependence-based reasons for smoking. Hence they were used in the computation of the Addiction Index.

The current SMQ analysis revealed a ten-factor structure. This was compared with Russell et al.'s (1974) six-factor structure. SMQ results were less consistent with original factor structure compared to the RFS, but still had many common factors and features of the original findings. The main six factors yielded here were highly similar to those of Russell et al. (1974); "Psychosocial", "Stimulation", "Addiction", "Sedative" (labelled "Indulgent" in the original structure), "Sensori-motor" and "Automatic". Four particular items that would not load substantially on any of the main factors represented the remaining four factors. Two of these single-item factors loaded on the major factors found by Russell et al. (1974), while the other two were not described by the original factor structure at all.

Comparisons can readily be drawn between the original SMQ "Addictive smoking" factor (Russell et al. 1974) and the "Addiction" factor elicited in this current SMQ analysis. In both analyses, questionnaire items 9 (running out of cigarettes being unbearable), 10 (automatic smoking), 17 (aware of periods of not smoking) and 31 (hunger to smoke following abstinence period) loaded on this factor. These were items Russell et al. (1974) had taken directly from the Ikard et al. (1969) report, and (as can be seen from Tables 2.1 and 2.2) these items loaded on the "Addiction" factor of the RFS.

Item 7 loaded on the "addiction" factor in the original analysis, but failed to reach the 0.5 threshold in this study (0.48). Item 24 loaded unexpectedly in the original report (0.42), but not so markedly here (0.37). The two factor structures for the SMQ are somewhat consistent. Like the RFS, factor scores from the SMQ "Addiction" factor were considered to be a valuable and effective tool in quantifying nicotine dependence, since they cumulatively measure subjects' addiction- or dependence-based reasons for smoking. Hence they were also used in the computation of the Addiction Index.

The general levels of nicotine tolerance in this sample were lower than those found in previous research. Mean FTQ scores in Fagerström's (1978) original paper were 6.2 and 7.2, compared with 3.9 in the current study. This difference is likely to be due to sample differences. Fagerström's (1978) subjects were clients at a smoking withdrawal clinic rather than predominantly undergraduates; they were also older and were heavier smokers than those in the current sample. The distribution of FTQ scores mirrors the negative skew distributions inferred by the "Addiction" factor scores of the SMQ and RFS. This was corroborated by the significant Spearman's correlations between FTQ and the two "Addiction" factors. This suggested that tolerance and addiction/dependence-based motivation to smoke were linked. These results are interpreted as suggesting that increased tolerance leads to increased addiction-based motivations to smoke. Hence FTQ scores were also used in the computation of the Addiction Index.

Combining weighted scores derived from the "Addiction" factors of the RFS and SMQ and weighted total FTQ scores created the Addiction Index. This is the first

composite multi-source smoking-dependence scale of its kind. The frequency distribution was negatively skewed, probably due to the large number of undergraduates in the sample. This may have meant the inclusion of a large number who have smoked for a relatively short time period and thus have not developed tobacco dependence or are in a transitional phase. Also, many students may be simply 'social smokers'; i.e. having one or two cigarettes a day whilst out drinking with peers, etc. The emergence of a bi-modal distribution of addiction index scores represents an exciting finding in tobacco research.

Although in essence nicotine dependence could be conceived as being on a continuum, it is shown here there are at least two definable subgroups of smokers in early adulthood. The relative sizes of the groups reflect the large sample skew better than the initial Addiction Index and median split division.

It must be appreciated that what are termed "non-addicted smokers" in this research does not necessarily equate with "chippers". The latter refers to a group that not only has a sparse and erratic smoking style, but is also characterised by an absence of withdrawal symptoms in abstinence. At the time of this initial data collection, susceptibility to withdrawal and severity and profile of symptom data were not available, but these data are discussed in Chapter 6. It was assumed that the withdrawal profile would not necessarily be associated with pre-abstinent behaviour patterns (e.g. smoking less than five cigarettes per day) therefore the term "non-addicted smoker" was used instead.

Furthermore, ascertaining true "non-dependence" requires evidence of stable regular low-level smoking over a considerable period. It may be that moderate levels of dependence coupled with reporting biases could lead to false categorisation. Smokers who have recently been trying to cut down, or who have recently started smoking and are just instantiating smoking behaviour patterns may also be erroneously categorised as "chippers" (Shiffman, 1989). These groups are in transitional phases, and therefore should not be called "chippers" in the true sense, rather "non-addicted smokers". This much more generic category can accommodate both "chippers" and low-level smokers in transitional phases of smoking behaviour. For investigative purposes of the research "non-addicted" is a functional category, although care must be taken drawing conclusions from data generated by this heterogeneous group.

Removing subjects' self-reported "addiction status" from the Addiction Index computation was performed for reasons highlighted in the previous section. The disparity between objective and subjective assessments of addiction are borne out by the results, as 68% of the non-addicted smokers reported being addicted to smoking. This large figure may be partly due to ambiguity or subjectivity about the meaning of "addiction". Alternatively, less dependent smokers may be claiming to be in the grip of nicotine addiction as a means of reducing cognitive dissonance or obscuring/denying other reasons for smoking that may have a more internal locus of control.

The addicted smokers group was predominantly male, whereas the non-addicted smokers were mainly female. This is broadly consistent with previous findings. Shiffman (1989) showed a trend to have greater proportions of males in the dependent

smokers group and more females in the chippers group. Subsequent research examining chippers has been heavily female-oriented since many studies used matched groups, and the apparent majority of chippers recruited are women (Kassel et al. 1994; Brauer, Hatsukami, Hanson & Shiffman, 1996). Furthermore, both Ikard et al. (1969) and Russell et al. (1974) found trends for females to have lower (RFS and SMQ respectively) "Addiction" factor scores than males. Explanations for these differences are unclear, although previous research showed that males smoke more cigarettes, smoke cigarettes with higher tar and nicotine content, inhale more frequently and more deeply than females (Waingrow, Horn & Ikard, 1968).

The addicted smoker group was associated with increased smoking when consuming caffeine. This is broadly consistent with previous research demonstrating a positive correlation between caffeine and nicotine intake (Istvan & Matarazzo, 1984; Budney, Higgins, Hughes & Bickel, 1993). Addicted smokers may be deriving enhanced positive effects of smoking through concurrent caffeine use (Chait & Griffiths, 1983), or the use of caffeine may be increasing smoking frequency (Emurian, Ellis, Brady & Ray, 1982), possibly through accelerating nicotine metabolism (e.g. Tanda & Goldberg, 2000). Animal studies provide evidence of interaction effects of the two substances that may partly explain their commonly concurrent use. Chronic caffeine exposure has been shown to alter the subjective reinforcing effects of nicotine in rats, thus enhancing its addictive potential (e.g. Tanda & Goldberg, 2000). How these effects are brought about is unclear, although caffeine may increase the dopaminergic action of nicotine (Shoiab, Swanner, Yasar & Goldberg, 1999). The coincidence of the two activities may be in part explained by environmental constraints and opportunities: e.g. break-times during a working day.

Caffeine antagonises adenosine A2 receptors; stimulation of these receptors inhibits dopaminergic activity as indicated by reductions in dopamine receptor binding (Hillefors-Berglund et al. 1995) and increases in locomotor activation and conditioned place preference (Brockwell & Beninger, 1996). However, the association observed in the current study may be due to group differences in baseline tea and coffee consumption. Unfortunately these data were not acquired, so this explanation cannot be ruled out.

No association was found between addiction group and increased smoking when consuming alcohol. All smokers reported increasing smoking when drinking. This is consistent with some previous research demonstrating a positive correlation between alcohol and nicotine intake (Istvan & Matarazzo, 1984; Schumann, Hapke, Rumpf, Meyer & John, 2001). As with caffeine and smoking, alcohol and tobacco are very often used concurrently. Again, animal studies offer some explanations as to why this might be. Reports have suggested that ethanol and nicotine produce combined effects on the mesolimbic dopamine pathway (Tizabi, Copeland, Louis & Taylor, 2002). This may explain why many heavy smokers also have high alcohol intakes (Istvan & Matarazzo, 1984), and why there is such a high incidence of smoking in alcoholics (e.g. Miller & Gold, 1998).

This does not explain why non-addicted smokers should derive a high benefit from concurrent use of the drugs. It is possible that alcohol-induced disinhibition leads to increased smoking, or that environmental cues (e.g. sitting in a pub) may prime the behaviours. Although experimental and anecdotal evidence suggests people may experience heightened euphoria from using alcohol and nicotine together rather than

individually (Perkins, Sexton, DiMarco, Grobe, Scierka & Stiller, 1995), human and animal work suggests that nicotine may counteract some of the cognitive performance deficits associated with alcohol intoxication (Kerr, Sherwood & Hindmarch, 1991; Gould, Collins & Wehner, 2001). Thus it may be that all smokers derive a variety of benefits from the stimulant effects of smoking when drinking alcohol.

Addicted smoker status was not associated with smoking more during the daytime than the evening. This was not predicted, since Fagerström (1978) showed that smokers who had higher nicotine tolerance were likely to smoke cigarettes during the daytime, particularly the morning, in order to boost plasma nicotine levels following overnight abstinence. This result is consistent with findings of other previous research, however. Shiffman (1989) showed no differences between chippers and dependent smokers in the distribution of smoking by time of day. This may be explained by the absence of chippers putatively fundamentally "social smoking"; if chippers or non-dependent smokers were simply social smokers a different temporal smoking pattern might be expected. However, Shiffman (1989) reported that chippers were as likely as dependent smokers to smoke alone, and no more likely to smoke when others are smoking. A similar explanation may account for the lack of association found between being an addicted smoker and having a partner who smoked.

The association between addicted smokers and parents' awareness that subjects smoked was a novel result. The findings may reflect the difficulty of hiding a very frequent behaviour from people who have a close relationship with the subject. Alternatively the result may be an artefact of the subject sample, as it was

predominantly undergraduates who have relatively short smoking histories. The last point is supported by the observation that mean age was higher in the addicted smokers group. Furthermore, older smokers may be less motivated to hide their tobacco habits from their parents as the dynamic of that relationship changes. A final explanation could pivot on the parents' own smoking behaviour. This hypothesis is supported by previous results suggesting that chippers are less likely than dependent smokers to have parents that smoke (Shiffman, 1989; Presson, Chassin & Sherman, 2002). Other research suggests that regular smokers are no more likely to have parents who smoke than chippers, but that close relatives of chippers are (if smokers) more likely to be chippers themselves (Kassel et al. 1994). This may mean that non-dependent smokers are less exposed to the smoking behaviours of their parents and are therefore less able to use their parents' habits as exoneration for their own. Unfortunately, parental smoking status data were not investigated by the SQB in the current study.

A positive correlation was found between levels of tobacco dependence measured by Addiction Index scores and agreement with positive belief statements about smoking. These included the sedative, stimulant and hedonic putative effects of smoking. There are few previous studies regarding the relative smoking beliefs of dependent and non-dependent smokers. Haddad & Malak (2002) found that Jordanian students who smoked had more positive attitudes toward smoking than non-smokers, and disagreed with some of the criticisms against smoking. It is likely that general beliefs regarding the effects of smoking may reflect subjects' own motivations for smoking, or vice versa. Shiffman (1989) found that dependent smokers had significantly higher factor scores than chippers on the "Negative affect", "Stimulation" and "Indulgent" factors

on the SMQ. These are interpreted as manifestations of sedative, stimulant and hedonic beliefs about smoking respectively. Shiffman's (1989) findings suggest that current subjects were expressing beliefs that are actually held rather than behavioural justifications simply arising from cognitive dissonance.

There are a number of methodological issues concerning this study. Unfortunately the cross-sectional sample yielded considerably more non-addicted smokers than addicted smokers. This was likely to have been due to the large number of undergraduates in the sample; they tended to have short smoking histories and/or smoking patterns structured by social patterns rather than tobacco dependence. It would have been preferable to improve the inclusiveness of the cross-section by recruiting more smokers from the general public. The Addiction Index could have been correlated with objective data regarding nicotine dependence (such as plasma nicotine levels, cue-reactivity or withdrawal sensitivity) by way of validating the scores generated. The SQB, although extensive, omitted several important questions.

Acquiring data regarding subjects' baseline alcohol and caffeine intake would have allowed more focused and confident interpretation of results regarding concurrent use of these substances with tobacco. Details regarding the subjects' family history of smoking would also have been useful. It is possible family history data may have discriminated between the addicted and non-addicted groups in its own right, or may have interacted with other items to be an important covariant in the analyses.

Using smoking motivation and nicotine tolerance self-report data, it was possible to create a tobacco Addiction Index scale from this sample of smokers. The resulting

profile allowed the sample to be split into groups labelled "addicted smokers" and "non-addicted smokers". In contrast to non-addicted smokers, addicted smokers were characteristically male, professed addiction to smoking, smoked more when consuming caffeine, and had parents who were aware of their habit. Disregarding the grouping, high scores on the Addiction Index were correlated with 1) smoking more cigarettes, 2) smoking sooner after waking, 3) having been a smoker for longer, and 4) having stronger positive beliefs about smoking. The generation of a functional multi-source tobacco dependence scale was critical to the subsequent studies. Once this was achieved, through frequency modelling and later re-evaluation two valid subgroups were derived based on smoking dependency status. The Addiction Index scale and "addicted"/"non-addicted" groupings are used throughout the rest of this research. In future this Addiction Index scale could chart the progression of smokers behaviour over time to identify whether individuals transmigrate between the two functional groups, and if so, how long it takes for this transition to occur.

Figure 2.1 Graph showing frequencies of subjects' Smoking Motivation Questionnaire "Addiction" factor scores.

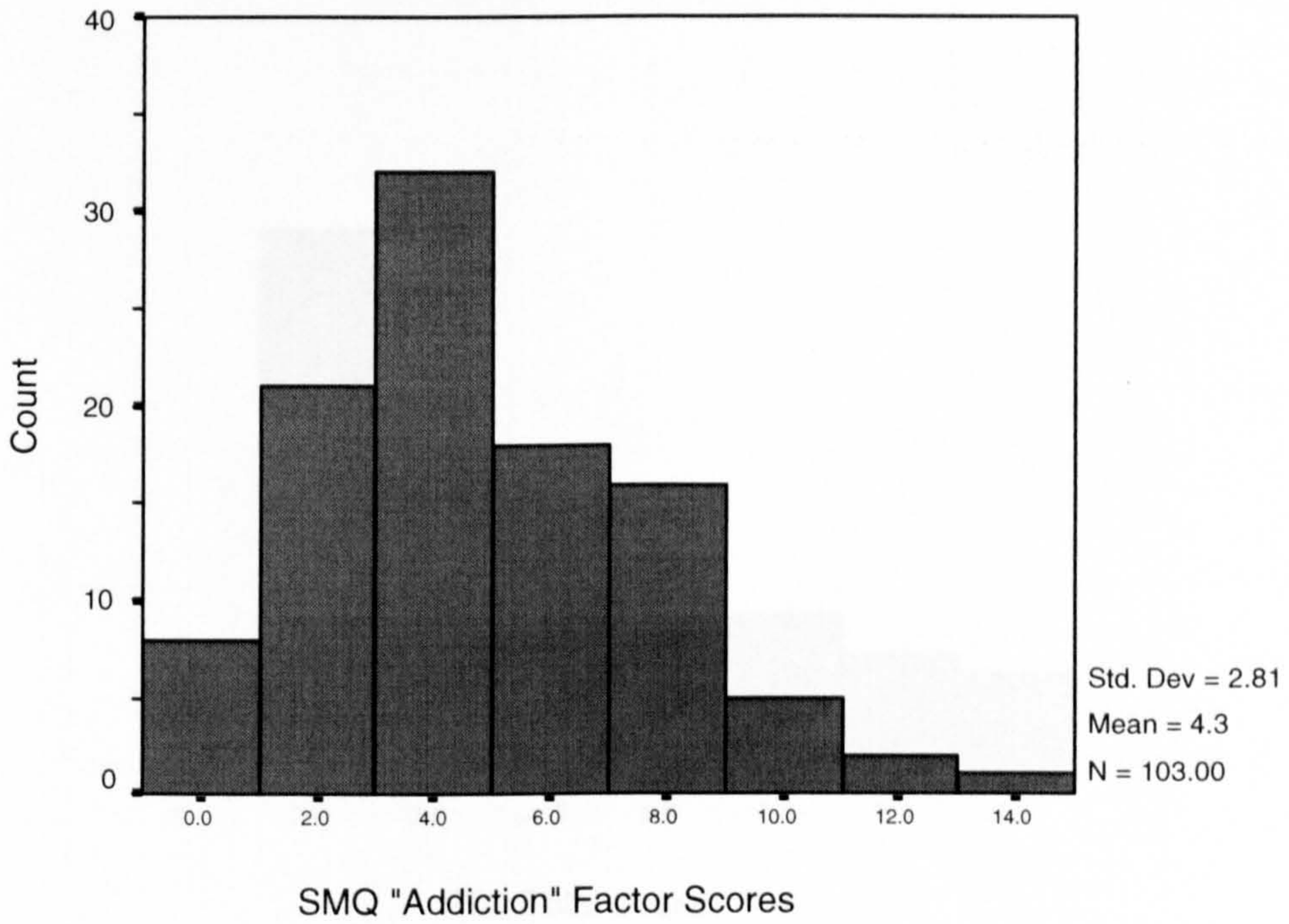


Figure 2.2 Graph showing frequencies of subjects' Reasons For Smoking scale "Addiction" factor scores.

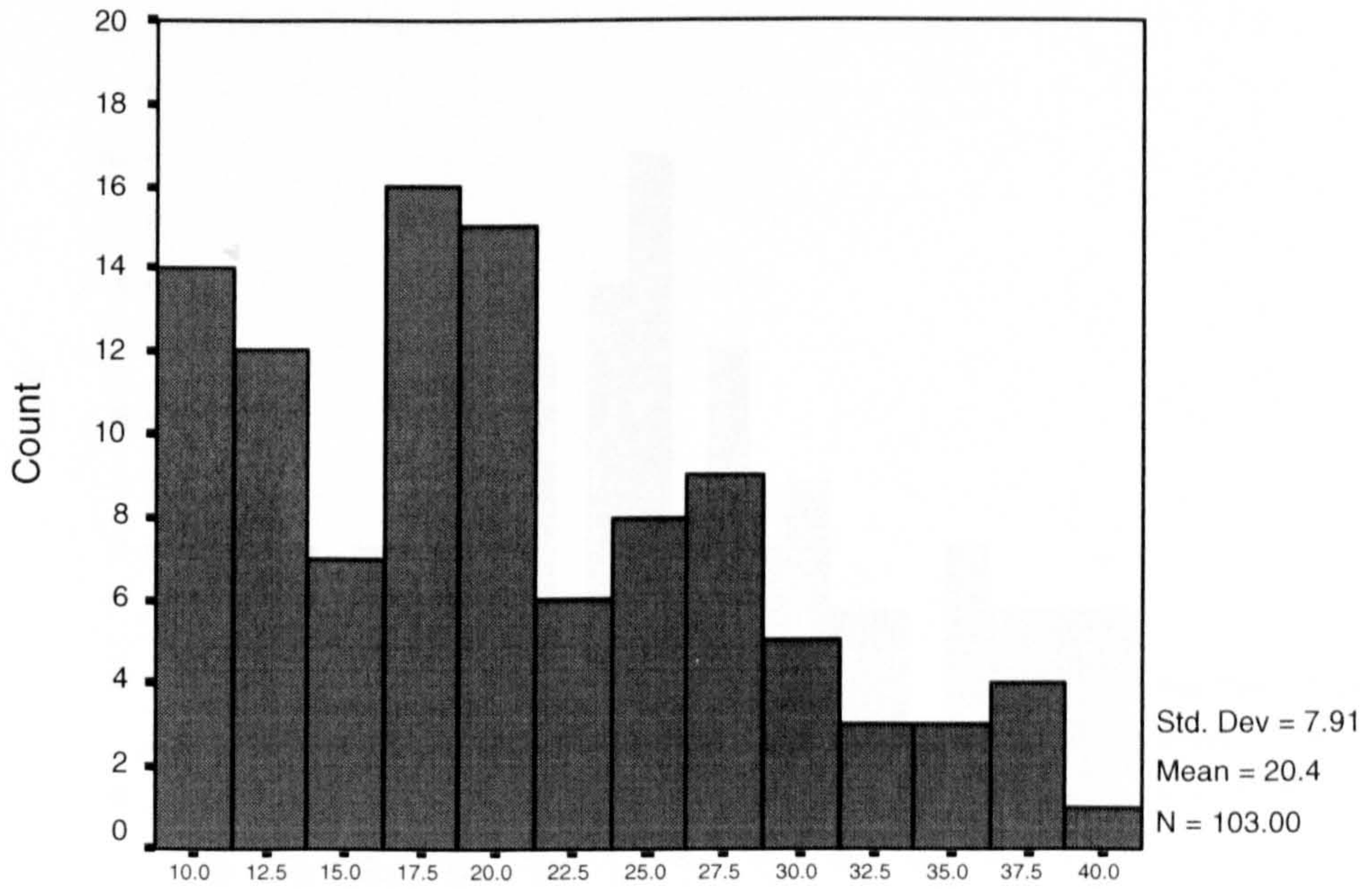


Figure 2.3 Graph showing frequencies of subjects' Fagerström Tolerance Questionnaire total scores.

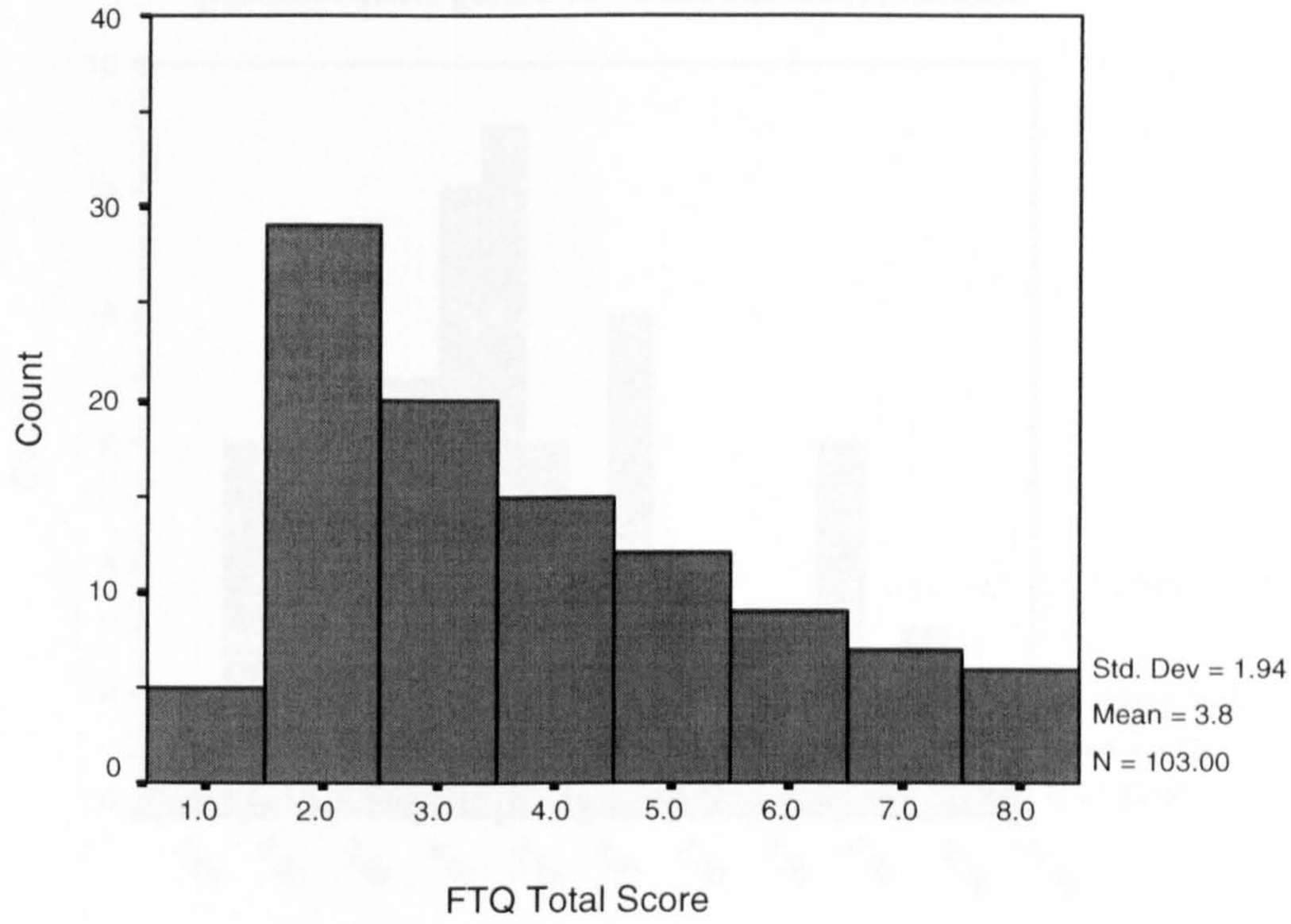


Figure 2.4 Graph showing frequencies of subjects' initial Addiction Index scores, incorporating self-assessment of addiction status.

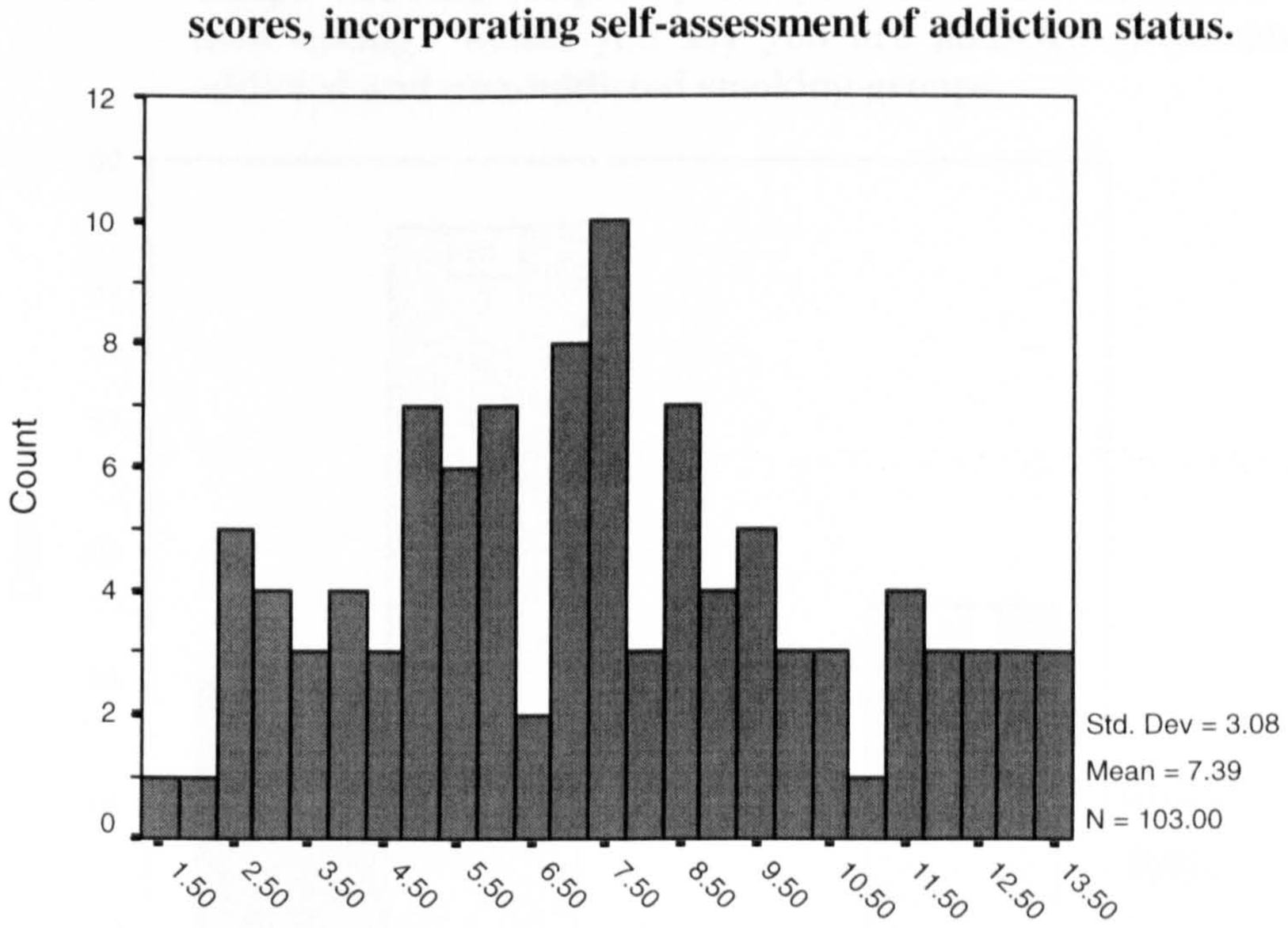


Figure 2.5 **Graph showing frequencies of subjects' final Addiction Index scores not incorporating self-assessment of addiction status, and possible emergence of bi-modal distribution.**

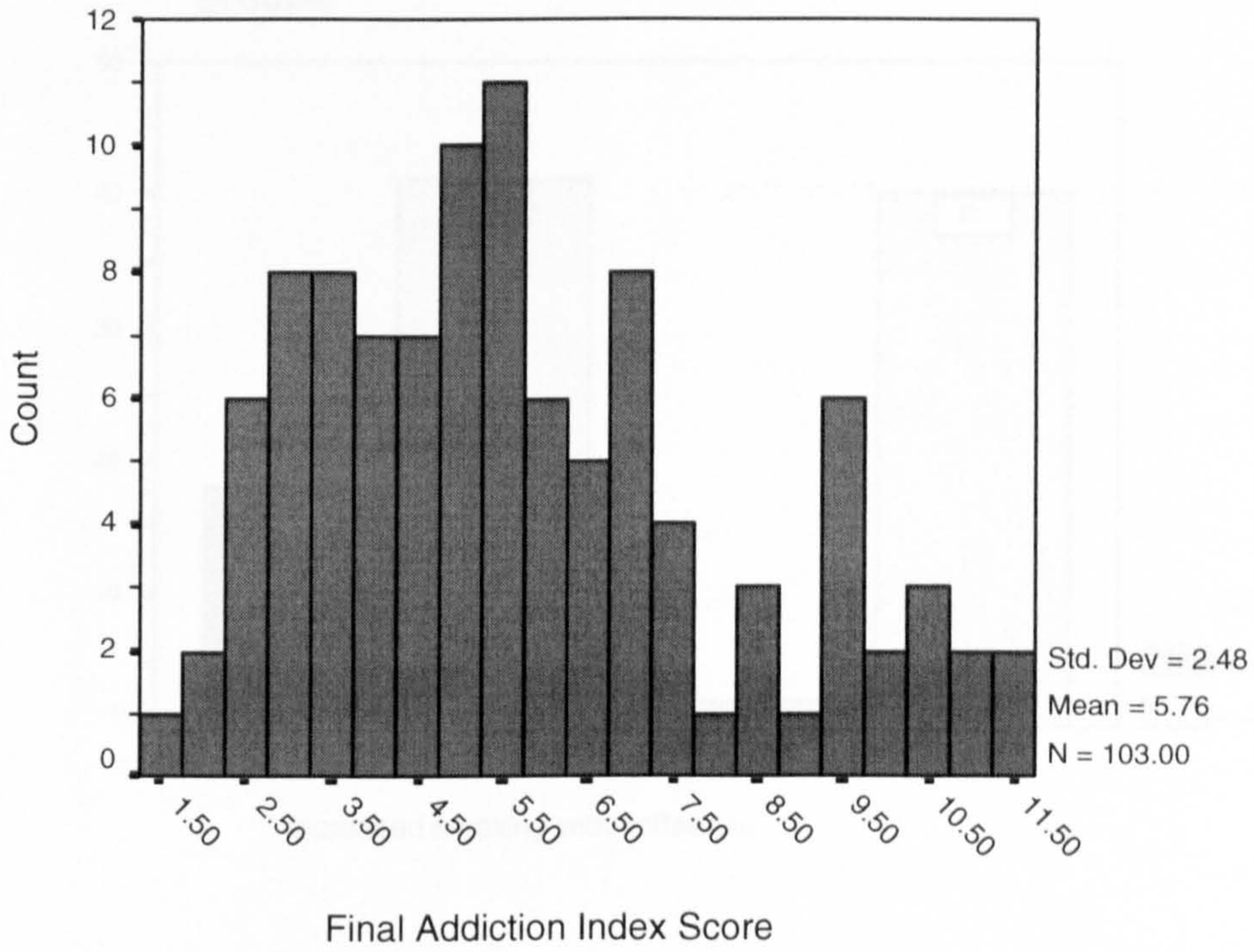


Figure 2.6 **Graph showing frequency of "yes" and "no" responses to SQB item asking "would you say you are addicted to smoking?" by addicted and non-addicted smoking groups.**

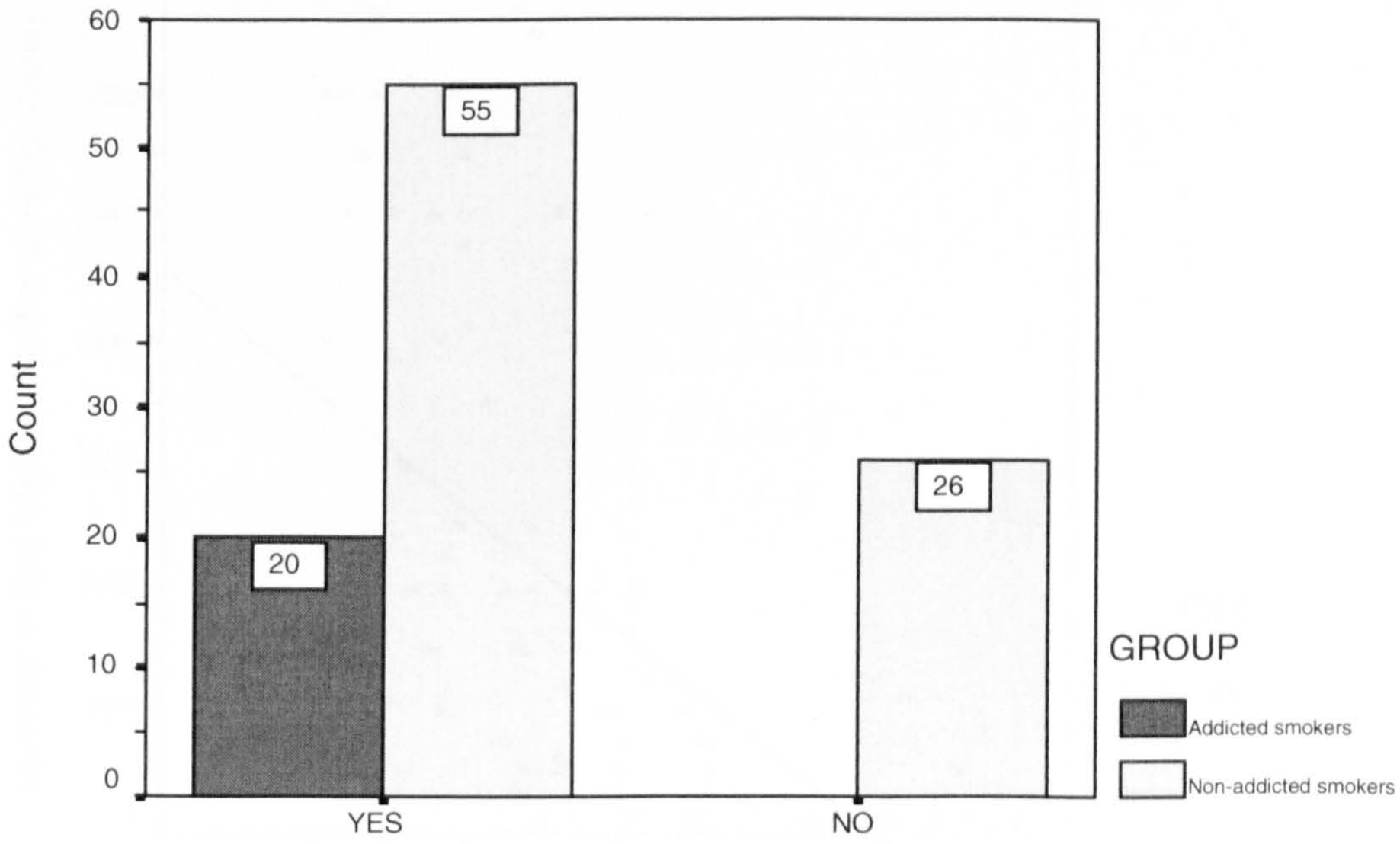


Figure 2.7 Graph showing frequency of "yes" and "no" responses to SQB item asking "do you find that you smoke more when you are drinking coffee or tea?" by addicted and non-addicted smoking groups.

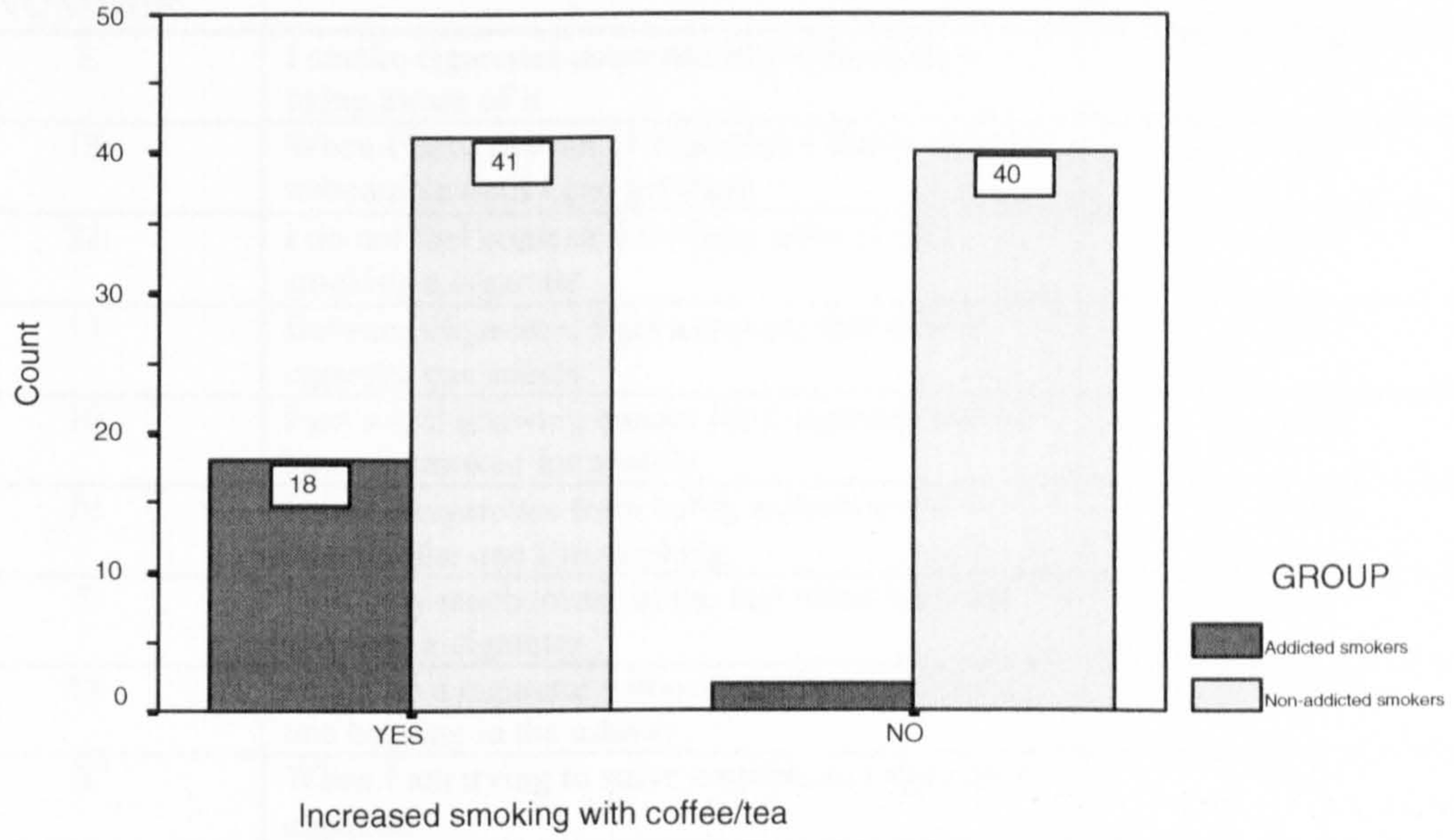


Figure 2.8 Scatterplot showing correlation between Addiction Index score and latency to smoking first cigarette after waking (minutes).

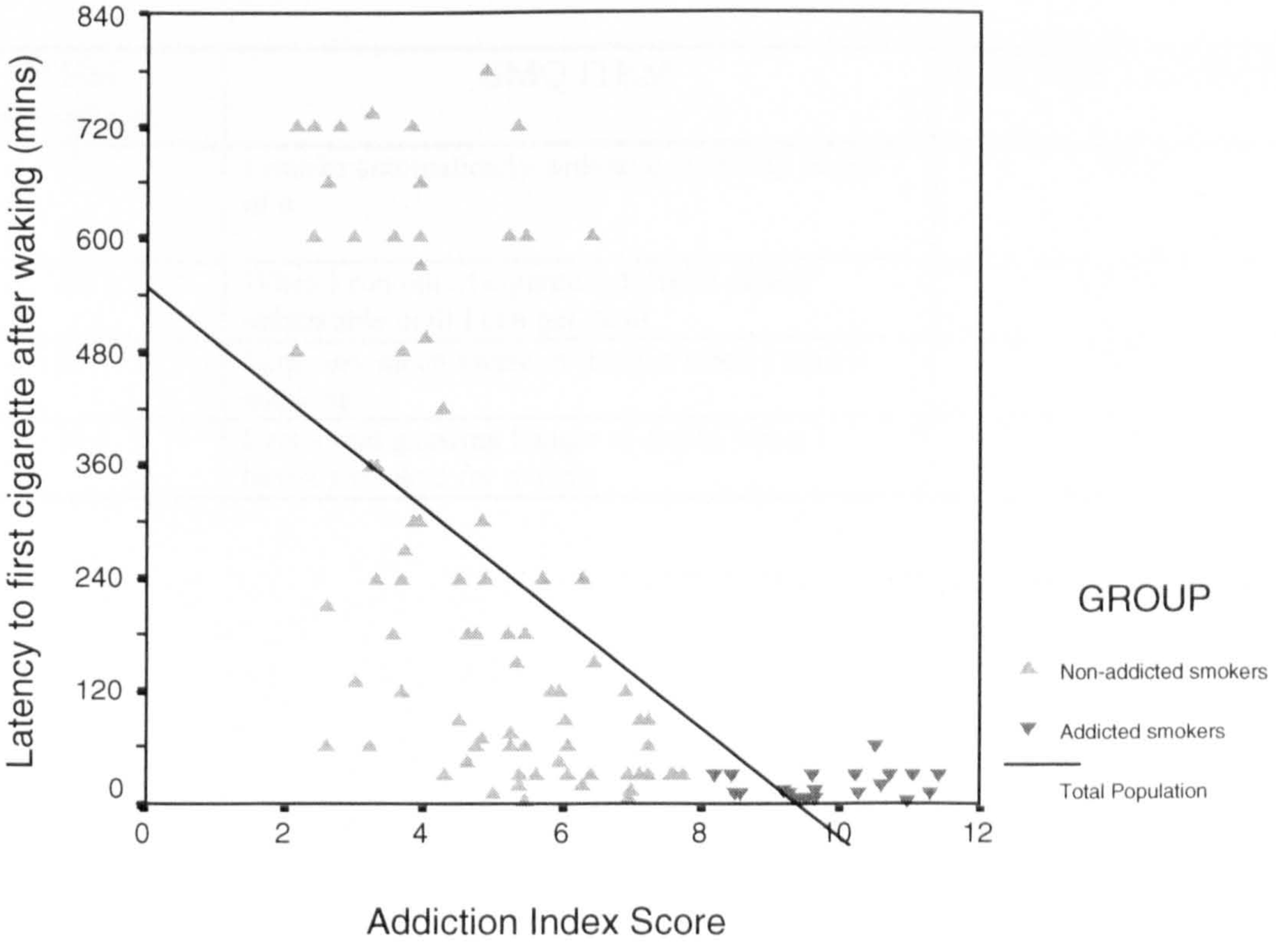


Table 2.1 Items loading on the Reasons For Smoking scale "Addiction" factor

ITEM NUMBER	RFS ITEM	FACTOR LOADING
8	I smoke cigarettes automatically without even being aware of it	0.87
18	When I have run out of cigarettes I find it almost unbearable until I can get them	0.75
22	I do not feel contented for long unless I am smoking a cigarette	0.73
13	Between cigarettes, I get a craving that *only* a cigarette can satisfy	0.71
10	I get a real gnawing hunger for a cigarette when I haven't smoked for a while	0.71
20	I smoke cigarettes from habit, without even wanting the one I'm smoking	0.66
5	I am very much aware of the fact when I am not smoking a cigarette	0.65
15	I light up a cigarette without realising I still have one burning in the ashtray	0.62
3	When I am trying to solve a problem, I light up a cigarette	0.55
4	When I smoke a cigarette, part of the enjoyment is watching the smoke as I exhale it	0.54

Table 2.2 Items loading on the Smoking Motivation Questionnaire "Addiction" factor

ITEM NUMBER	SMQ ITEM	FACTOR LOADING
10	I smoke automatically without even being aware of it	0.81
9	When I run out of cigarettes I find it almost unbearable until I can get them	0.74
17	I am very much aware of the fact when I am not smoking	0.66
31	I get a real gnawing hunger to smoke when I haven't smoked for a while	0.63

Table 2.3 Mean and standard deviations of "Addiction" factor scores and responses to specific demographic and smoking behaviour questions in the Smoking Questionnaire Battery for addicted and non-addicted smoker groups

Item \ Group	NON-ADDICTED SMOKERS	ADDICTED SMOKERS
Mean (SD) age (years)	24.51 (13.04)	28.67 (17.58)
Mean (SD) age when started smoking (years)	15.94 (2.21)	14.67 (4.39)
Mean (SD) number of cigarettes smoked per day**	5.91 (11.30)	20.40 (6.39)
Mean (SD) latency to first cigarette of the day (minutes)**	243.51 (203.02)	18.48 (14.43)
Mean (SD) number of attempts to quit smoking	1.44 (2.06)	1.15 (1.49)
Mean (SD) SMQ "Addiction" factor score*	3.37 (1.99)	7.86 (2.69)
Mean (SD) RFS "Addiction" factor score*	17.86 (5.80)	30.14 (8.22)
Mean (SD) FTQ total score*	3.19 (1.40)	6.29 (1.93)

*These scores were used in generating the Addiction Index score to create the groups
**These questions were asked in categoric form in the FTQ

Table 2.4 Percentage responding affirmatively to specific demographic and smoking behaviour questions in the Smoking Questionnaire Battery for addicted and non-addicted smoker groups

Item \ Group	NON-ADDICTED SMOKERS	ADDICTED SMOKERS
Percentage who "would say they are addicted to smoking"	67.9	100
Percentage of male participants in the group	65	38
Percentage whose parents know they smoke	58.8	89.5
Percentage who smoke more in the daytime than evening	15.6	25
Percentage who smoke more when they drink coffee/tea	50.6	90
Percentage who smoke more when they drink alcohol	96.3	95
Percentage who smoke more when they drink soft drinks	8.6	15
Percentage of subjects with partners who smoke (if they had partners)	56.9	70

Table 2.5 Mean and standard deviations of agreement scores (range 0 – 4) for addicted and non-addicted smoker groups on items in the Smoking Beliefs Inventory

Statement \ Group	NON-ADDICTED SMOKERS	ADDICTED SMOKERS
Mean (SD) agreement to "smoking can help people relax" (0-4)	3.12 (0.80)	3.48 (0.98)
Mean (SD) agreement to "smoking is a dirty habit" (0-4)	2.89 (1.30)	2.38 (1.40)
Mean (SD) agreement to "smoking can help people when they feel nervous or embarrassed" (0-4)	3.02 (0.79)	3.24 (1.00)
Mean (SD) agreement to "smoking improves concentration" (0-4)	1.89 (1.20)	2.38 (1.02)
Mean (SD) agreement to "smoking does more harm than good" (0-4)	3.49 (0.91)	3.38 (1.12)
Mean (SD) agreement to "smoking improves memory" (0-4)	1.16 (1.05)	1.33 (1.11)
Mean (SD) agreement to "children should be discouraged from smoking" (0-4)	3.60 (1.06)	3.38 (1.43)
Mean (SD) agreement to "smoking is a nuisance" (0-4)	2.63 (1.11)	2.00 (1.34)
Mean (SD) agreement to "smoking is pleasurable" (0-4)	3.20 (0.84)	3.24 (1.14)
Mean (SD) agreement to "smoking can kill" (0-4)	3.89 (0.55)	3.19 (1.36)

Chapter 3 – Mood and cognitive performance changes in nicotine withdrawal and subsequent reinstatement in addicted and non-addicted smokers

3.1 Introduction

A variety of negative changes in psychological state or function occur when dependent smokers abstain from smoking. This has been conceptualised as the *tobacco withdrawal syndrome*, and is described in DSM-IV. The syndrome includes symptoms such as craving for tobacco, irritability, restlessness and impairment on tasks requiring concentration (e.g. Hatsukami, Hughes & Pickens, 1985). This latter symptom is based on a large number of studies demonstrating that smokers do more poorly on some tasks when deprived of cigarettes as compared to a non-deprived smoking group (Wesnes & Warburton, 1983b).

Tobacco withdrawal has been demonstrated to cause impairments in cognitive function, although these are not uniform across different measures. Heimstra et al. (1980) reported performance deficits on a psychomotor task following 24-hour cigarette deprivation. Other research has shown that tobacco deprivation had no effect or impaired performance on simple tasks (e.g. vigilance) (Elgerot, 1976; 1978) and had no effect or enhanced performance on complex tasks (e.g. mental arithmetic) (Myrsten, Elgerot & Edgren, 1977). Snyder & Henningfield (1989) reported that smokers who abstained from tobacco for 12 hours performed more poorly on a variety of cognitive tasks than they did under *ad libitum* smoking conditions. Snyder, Davis

& Henningfield (1989) reported that tobacco deprivation significantly increased response latencies on five and decreased accuracy on two cognitive performance tests. The impairments peaked at 24-48 hours before returning toward baseline (non-deprived) levels. Snyder et al. (1989) also showed that these impairments were partially reversed after 1 hour of resumption of smoking, with all impairments returning to baseline levels within 24 hours of resumption of smoking.

Abstinence from tobacco is associated with negative changes in mood in dependent smokers, hence the inclusion of symptoms such as irritability, anxiety and impatience in the withdrawal syndrome. Shiffman et al. (1995) reported that dependent smokers experience decreased arousal and increased mood disturbance, such as lowered hedonic tone, when withdrawn from tobacco.

Previous studies suggest that smoking motivation factors may predict severity of nicotine withdrawal symptoms, and thus level of dependence or addiction (e.g. West & Russell, 1985). There is evidence of a sub-group of regular or habitual smokers – called "chippers" - who seem able to tolerate prolonged periods of abstinence with no overt or reported withdrawal symptoms (Shiffman, 1989). It is still unclear what mechanism allows these individuals to regularly self-administer nicotine - a highly addictive drug - without developing dependence as in the majority of smokers consuming comparable levels of the substance. Shiffman et al. (1995) examined the differences between chippers and dependent smokers during 48-hour periods of either smoking or abstinence. They found that chippers showed no changes in tobacco withdrawal, either in terms of self-report ratings of withdrawal symptoms or cognitive

performance, whereas dependent smokers task performance was slower when in abstinent conditions. Controversially, their overall results were conceptualised as demonstrating nicotine enhancing performance rather than withdrawal-mediated impairments.

The aim of this study was to examine possible differences in changes of mood and cognitive performance, following nicotine withdrawal and reinstatement, between addicted smokers and non-addicted smokers. The predicted impairments to cognitive performance are indices of acute psychopharmacological changes and markers of withdrawal in their own right. Two hypotheses were examined:

I. that addicted smokers will be more negatively affected by 24-hour nicotine withdrawal in terms of mood and cognitive performance compared with non-addicted smokers.

II. that nicotine reinstatement will positively affect mood and cognitive performance of addicted smokers more greatly than non-addicted smokers.

3.2 Method

3.2.1 Design

The study was a mixed design investigating three groups (N=75) comprising non-smokers (n=25), addicted smokers (n=10), and non-addicted smokers (n=40), as defined in Chapter 2. Subjects completed computer-based mood scales and cognitive tasks in three different sessions ("Baseline", "Withdrawn" and "Reinstated"). Fifty-

nine smokers who completed the Smoking Questionnaire Battery (see Chapter 2) did not participate in this experiment.

The smokers were grouped as 'addicted' or 'non-addicted' following the completion of all questionnaires and performance trials. Grouping was achieved by computing the "Addiction Index" for each smoker, as described in Chapter 2.

3.2.2 Subjects

Subjects were recruited from a database at the Health Psychology Research Unit, University of Bristol. Recruitment posters placed in University departments, e-mails to student mailing lists and verbal communication, supplemented this database. The majority of subjects completing the Smoking Questionnaire Battery (n=109) were undergraduate or post-graduate students. The remaining subjects were recruited from outside the University. From this initial screening 50 smokers took part in this study. Non-smokers (n=25) were recruited in a similar manner to smokers. Non-smokers did not complete the Smoking Questionnaire Battery and were not breathalysed prior to the "withdrawn" session, as it was considered unnecessary. Subjects were paid £50, except non-smokers who received £30 since they were not paid for the inconvenience and discomfort of abstinence.

3.2.3 Questionnaires

Withdrawal Symptoms Checklist (WSC; Hughes & Hatsukami, 1986) and Questionnaire of Smoking Urges (QSU; Tiffany & Drobes, 1991) were administered to subjects as part of the procedure. Due to the large amount of data this study

generated this chapter concentrates on the cognitive performance and visual analogue mood scale data. Data from the WSC and QSU questionnaires are presented and discussed in Chapter 6.

3.2.5 Computer tasks

The computer test battery was derived from Broadbent's (1984; et al. 1984) human performance measurement system. Duration was the same for all experimental sessions. Tasks were always in the same order (with self-report mood scales at the beginning and end, and the eight cognitive performance tasks between), although target stimuli or data sets were changed for each of the sessions. The tests used are listed and briefly described below. These particular tests have been extensively used and validated (e.g. Smith, Wilson, Glue & Nutt, 1992).

Mood 1

Subjects rated their current mood on 18 consecutively presented bi-polar visual analogue scales. These scales consisted of a horizontal line with extremes of emotion at either end (e.g. DEPRESSED and ELATED), and a short vertical bisect which subjects moved using the left and right keys on the control box to indicate on the scale how they felt at that moment. Each of the 18 items in the mood scales generated a score between 1 and 51. These items factorised onto three scales. Factor 1 (Alertness), Factor 2 (Hedonic Tone) and Factor 3 (Anxiety) were examined. See Appendix V.

Simple reaction time

Subjects were presented with 5 minutes of trials on this task. In this task a frame of a box was displayed in the centre of the screen and at varying intervals (from 1-8 seconds) a target square appeared inside the box. As soon as participants detected the square, they were required to press the response key marked SPACE using the forefinger of their dominant hand only. Reaction times below 200 milliseconds or greater than 750 milliseconds were eliminated from the raw data. See Appendix VI.

Focused attention

Subjects were presented with ten practice trials followed by 5 blocks of 64 trials (approximate duration of 6 minutes) on this task. In this task, target letters ('A' or 'B') appeared in the centre of the screen. Participants responded to the target in the *centre* of the screen as quickly and accurately as possible, ignoring any distracters. Warning crosses were presented on the screen for 500 ms, before being replaced by the target letter. The central target letter was either accompanied by 1) nothing, 2) asterisks, 3) letters that are the same as the target or 4) letters that are different from the target. See Appendix VII.

Categoric search/ divided attention

Subjects were presented with ten practice trials followed by 5 blocks of 64 trials (approximate duration of 6 minutes) on this task. Two crosses were presented for 500 ms either in the near location, or further towards the left and right extremes of the screen. The target letter then appeared in place of one of these crosses. In 50% of

trials the target letter 'A' or 'B' is presented alone, and in 50% of trials it is presented with a distracter (single digit). See Appendix VIII.

Psychomotor (5-choice)

This task lasted 5 minutes, and provided a measure of both speed and accuracy of movement to a choice of targets. Subjects were presented with five LED buttons arranged in a regular pentagon shape, with a sixth in the centre. They were required to switch each button off by pressing it as soon as it lit up. Only one button would be lit at any one time, and extinguishing a peripheral button would light the central one, and vice versa. See Appendix IX.

Repeated digits detection RVIP/ vigilance task

This visual cognitive vigilance task measures the ability to detect targets at irregular intervals. In this task lasting 5 minutes, participants were shown successive presentations of three digit numbers in the centre of the screen at the rate of 100 per minute. Each three-digit number usually differed from the one immediately preceding it, with one out of the three digits being replaced with a different digit (e.g. 463, 563, 562). Eight times per minute the same three-digit number will be presented on successive trials. Participants were required to detect and respond to these repetitions as quickly as possible by pressing a key. See Appendix X.

Mood 2

Subjects repeated the visual analogue mood scales presented at the start of the battery.

3.2.4 Procedure

Subjects were given written information and consent was obtained. They were required to attend the Health Psychology Research Unit (HPRU) on a minimum of two occasions. Four sessions of computer-administered cognitive tasks were to be completed - Familiarisation, Baseline, Withdrawn and Reinstated. The latter two sessions were always performed consecutively.

Familiarisation

All subjects completed this 20-minute session prior to Baseline. This session consisted of shortened versions of the tasks utilised in the experimental sessions. On completion, subjects were invited to ask questions, and investigators checked data to ensure tasks were being performed correctly.

Baseline

Subjects attended the HPRU at 9.00 am, having been instructed to:

a) Smoke *as they normally would* both in the previous evening and in the morning before attending the Unit.

b) Refrain from excessive alcohol intake (>4 units) during the previous evening.

c) Consume normal caffeine intake before attending the Unit, up to 20 minutes prior to arrival.

d) Have a typical sleep pattern during the preceding night.

e) Not exercise vigorously in the morning before attending the Unit.

9.00am. On arrival, subjects were shown to a booth and asked to complete the Baseline Session Pre-test Questionnaire. This booklet contained questions regarding eating, drinking and smoking behaviour in the last 24 hours, a Withdrawal Symptoms Checklist, and Tiffany & Drobes (1991) Questionnaire of Smoking Urges. These data are discussed in Chapter 6.

9.10am. Participants were asked to supply a DNA sample (see Chapter 4).

9.15am. Subjects then performed the full version of the battery of computer tasks. This took approximately 50 minutes.

10.10am. Participants reminded of their appointment for the next session and of their abstinence requirements for that stage.

10.15am. Subjects left HPRU.

Withdrawn

Subjects attended the HPRU at 9.00 am, having been instructed to:

a) Smoke *nothing* in the preceding 24 hours before attending the Unit, and follow the conditions b) to e) as for the Baseline session.

9.00am. On arrival, subjects were breathalysed using a carbon monoxide breathalyser. If <10 PPM (parts per million) CO count, then abstinence was assumed and the procedure was continued. Subjects were also asked to report if they had lapsed (smoked) during the abstinence period. These details were recorded.

9.05am. Subjects completed the Withdrawn Session Pre-test Questionnaire (see Chapter 6).

9.15am. Subjects then performed the full version of the battery of computer tasks. This took approximately 50 minutes.

10.10am. Upon completion of the computer tests by all participants in the laboratory, subjects were informed they had an hour before the final session. They were issued with ashtrays and advised that they could smoke at least 1 cigarette during the next 45 minutes. Participants smoked between 1 and 5 cigarettes in this period. During this hour, subjects were administered Cloninger's (1992) Temperament & Character Inventory (see Chapter 4). No caffeine or eating was permitted during this period, and subjects generally passed time reading. After 45 minutes, subjects were asked to extinguish any cigarettes and relax. Once the hour break was concluded, the next session commenced.

10.55am. Subjects were asked to extinguish any cigarettes and relax.

11.10am. Next session commenced.

Reinstated

11.10am. Subjects then completed the Reinstated Session Pre-test Questionnaire. This booklet consisted of questions regarding eating, drinking and smoking behaviour in the last hour, a withdrawal symptoms checklist, Tiffany & Drobes (1991) Questionnaire of Smoking Urges. Subjects then performed the full version of the battery of computer tasks. This took approximately 50 minutes.

3.2.6 Statistical analysis

Mood data was factorised to give scores on three axes (alertness, hedonic tone and anxiety).

Statistical analyses were performed using BMDP (Bio-Mathematics Data Processing, Release 7) statistical software package. Univariate analyses of variance (ANOVA) with Tukey post-hoc tests were performed on the change scores.

Correcting for multiple comparisons in the Focused Attention and Categoric Search tasks, since both tests examined large numbers of variables, was considered but not performed as it was deemed inappropriate. Although many statistical tests were performed in the analyses of both tasks, the precise variables tended to be highly correlated components of either accuracy or reaction time on the global cognitive attributes measured. Correcting for multiple comparisons would have therefore increased the likelihood of Type II error.

3.3 Results

3.3.1 Effects of withdrawal on mood and cognitive performance

Change scores were created for all variables in each cognitive test and mood rating by subtracting Baseline session scores from Withdrawn session scores. The mean change scores were then compared across the three groups (non-smokers, non-addicted smokers and addicted smokers).

An overview of the observed effects of tobacco withdrawal is shown in Table 3.1.

3.3.1.1 Mood

Neither Alertness or Hedonic Tone changes between Baseline and Withdrawn sessions were significantly different between the groups in either pre-test or post-test ratings.

Pre-test Anxiety change scores from Baseline to Withdrawn session did not differ significantly between the subject groups. Post-test Anxiety factor change scores were significantly different according to group ($F\{2,72\}=3.99$, $p<.025$). Addicted smokers reported increased post-test Anxiety following withdrawal, whereas the non-addicted smokers' Anxiety ratings decreased from baseline (see Figure 3.1). Non-smokers reported feeling slightly greater post-performance Anxiety in their second session. Lower scores on this factor indicated higher ratings on the mood scale items measuring Anxiety (relaxed-excited, troubled-tranquil, tense-calm). Tukey post-hoc analysis demonstrated that addicted smokers had significantly different changes in Anxiety to non-addicted smokers ($p<.05$), and a non-significant trend for greater increases in Anxiety than non-smokers ($p<.10$).

3.3.1.2 Cognitive Performance

3.3.1.2.1 Simple reaction time task

No significant group effects were yielded from analysis of variance on change scores (Withdrawn minus Baseline) for this simple reaction time task.

3.3.1.2.2 Focused attention task

A non-significant trend was observed for the groups to show different changes in accuracy responding to targets presented alone or with asterisks ($F\{2,72\}=2.99$, $p<.06$). Non-smokers change scores showed increased accuracy, while addicted and non-addicted smokers change scores showed decreased accuracy in the Withdrawn session (Figure 3.2). Tukey post-hoc analysis showed significant differences between non-addicted smokers and non-smokers change scores ($p<.05$).

3.3.1.2.3 Categoric search task

Change scores in the number of long responses (lapses) on the categoric search task following withdrawal were significantly different according to group ($F\{2,72\}=4.86$, $p<.025$). All groups showed a reduction in number of long responses from Baseline to Withdrawn sessions (Figure 3.3). The addicted smokers had a greater reduction in number of long responses than non-addicted smokers following withdrawal (Tukey post-hoc analysis, $p<.01$).

Non-smokers became faster at encoding new information between Baseline and Withdrawn conditions whereas both groups of smokers, particularly the addicted group, became slower ($F\{2,72\}=3.45$, $p<.05$) (Figure 3.4). Tukey analysis showed non-significant trend differences between non-smokers and both the addicted smokers and non-addicted smokers (both $p<.10$).

All three groups became faster responding to targets presented alone or with asterisks in the categoric search task in the Withdrawn session, with addicted smokers and non-

smokers demonstrating greater acceleration of reaction time than non-addicted smokers ($F\{2,72\}=4.66$, $p<.025$) (Figure 3.5). Tukey post-hoc analysis showed non-addicted smokers differed from non-smokers ($p<.05$) and from addicted smokers as a non-significant trend ($p<.10$).

3.3.1.2.4 Five-choice serial reaction time (psychomotor) task

No significant group effects were yielded from analysis of variance on change scores (Withdrawn minus Baseline) for this psychomotor task.

3.3.1.2.5 Repeated digits RVIP / Vigilance task

A non-significant trend was observed for group effects on changes following withdrawal in 'number of hits' (correct response to targets) on the repeated digits vigilance/RVIP task ($F\{2,72\}=2.57$, $p<.10$). All three groups demonstrated decreases in the number of 'hits' in the Withdrawn session compared to Baseline. The addicted smoker group was most affected, with a mean of approximately one less 'hit' (Figure 3.6). Tukey post-hoc test showed a non-significant trend of difference between addicted smokers and non-smokers ($p<.10$).

3.3.2 Effects of nicotine reinstatement following 24-hour withdrawal on mood and cognitive performance.

An overview of the observed effects of tobacco reinstatement is shown in Table 3.2.

Change scores were created for all variables in each cognitive test and mood rating by subtracting Withdrawn session scores from Reinstated session scores. The mean

change scores were then compared across the three groups (non-smokers, non-addicted smokers and addicted smokers).

3.3.2.1 Mood

A non-significant trend for group effects on changes in pre-test Alertness from Withdrawn session to Reinstatement session was observed ($F\{2,72\}=2.61$, $p<.10$). Both smoking groups rated their pre-test Alertness higher in the Reinstatement session than in the Withdrawal session, whereas non-smokers rated their alertness lower in their final session (Figure 3.7). Tukey post-hoc analyses showed a non-significant difference between non-smokers and non-addicted smokers ($p<.10$).

A significant group effect was shown on changes in post-test Alertness following reinstatement ($F\{2,72\}=5.23$, $p<.01$). Both smoking groups rated their post-test Alertness higher in the Reinstatement session than in the Withdrawn session, whereas non-smokers rated their alertness lower in their final session (Figure 3.8). Tukey post-hoc analyses showed differences between non-smokers and non-addicted smokers ($p<.01$), and a non-significant trend difference between non-smokers and addicted smokers ($p<.10$).

Pre-test Hedonic Tone change scores (from Withdrawn to Reinstatement session) did not differ significantly between the subject groups. Group effects were shown on post-test Hedonic Tone changes following reinstatement ($F\{2,72\}=3.88$, $p<.025$). Both smoking groups reported improved Hedonic Tone in the Reinstated session, whereas non-smokers reported decreased Hedonic Tone in their final session (Figure

3.9). Differences between non-smokers and non-addicted smokers were significant (Tukey post-hoc analysis, $p<.05$).

Pre-test Anxiety change scores (from Withdrawn to Reinstatement session) did not differ significantly between the subject groups. A non-significant trend was observed for group effects on changes in ratings of post-test Anxiety following reinstatement ($F\{2,72\}=2.49$, $p<.10$). Non-smokers and non-addicted smokers showed a slight increase in post-test Anxiety from withdrawal session to reinstated session. Addicted smokers demonstrated a large decrease in post-test Anxiety after reinstatement (Figure 3.10). Tukey post-hoc analysis showed a non-significant difference between addicted and non-addicted smokers ($p<.10$).

3.3.2.2 Cognitive Performance

3.3.2.2.1 Simple reaction time task

A significant group effect was demonstrated on total mean reaction time changes from Withdrawn session to Reinstated session in the simple reaction time task ($F\{2,72\}=7.12$, $p<.01$). All three groups became slower in the Reinstated session, although Tukey post-hoc analysis showed the non-smokers reaction times decelerate more than both the non-addicted smokers ($p<.01$) and (as a non-significant trend, $p<.10$) addicted smokers (Figure 3.11).

3.3.2.2.2 Focused attention task

No significant results were yielded from analysis of variance on differential changes following reinstatement on these groups for this task. It would therefore appear that

reinstatement following 24-hour nicotine withdrawal does not affect focused attention.

3.3.2.2.3 Categoric search task

Group effects were shown for changes following reinstatement on reaction time taken to encode new information in the categoric search task ($F\{2,72\}=5.36$, $p<.01$). The smoking groups both became faster at encoding new information following reinstatement, whereas the non-smokers became slower in their final session (Figure 3.12). Tukey post-hoc analyses showed non-smokers differed from both non-addicted smokers ($p<.01$), and non-significantly from addicted smokers ($p<.10$).

A non-significant trend for group effects was observed on changes following reinstatement on reaction time responding to targets presented alone or with asterisk in the categoric search task ($F\{2,72\}=2.45$, $p<.10$). All three groups became faster on these trials in the Reinstated session compared with Withdrawn session, but smokers (especially non-addicted) demonstrated the greatest improvement (Figure 3.13). All Tukey post-hoc comparisons were not significant.

3.3.2.2.4 Five-choice serial reaction time (psychomotor) task

No significant group effects were shown on changes following reinstatement for this task. It would therefore appear that reinstatement following 24-hour nicotine withdrawal does not affect psychomotor performance, as measured by the 5-choice serial reaction time task.

3.3.2.2.5 Repeated digits detection task

No significant group effects were shown on changes following reinstatement for this task. It would therefore appear that reinstatement following 24-hour nicotine withdrawal does not affect vigilance or RVIP, as measured by the repeated digits detection task.

3.4 Discussion

Acute 24-hour abstinence from smoking was shown to have a variety of effects on cognitive function and negatively affect mood. Subsequent reinstatement through 45 minutes of *ad libitum* smoking improved mood and cognitive performance, and in some cases reversed some of the withdrawal-induced deficits. Mood of addicted smokers was more adversely affected by tobacco withdrawal than the non-addicted group, demonstrated by a trend toward greater increases for addicted smokers than the non-addicted group in post-test Anxiety following withdrawal. There was a trend for reinstatement to cause greater reductions in post-test Anxiety in addicted smokers compared to non-addicted smokers,

Addicted smokers cognitive performance was somewhat more enhanced than the non-addicted smokers following withdrawal. Lapses (long response times) on the categoric search task were significantly reduced by withdrawal in the addicted smokers compared with non-addicted smokers. A trend was observed for addicted smokers to be more accurate following withdrawal than non-addicted smokers on categoric search trials with neutral or no distracters. Few variables were differentially affected by reinstatement according to smoking group. Non-addicted smokers

experienced more accelerated reaction times on categoric search trials with neutral or no distracters.

In terms of cognitive performance, nicotine withdrawal through 24-hour abstinence from smoking produced a variety of effects. There was a trend for smokers to perform less accurately in withdrawal on trials in the focused attention task. This contrasts with Snyder et al.'s (1989) findings, as they reported withdrawal affecting reaction time rather than accuracy on simple tasks. All subjects experienced fewer attentional lapses (long reaction times) in the categoric search task in the Withdrawn session. This was not predicted by the hypotheses, since lapses indicate loss of concentration, which was expected to occur, particularly in the addicted smokers. This finding is difficult to explain, but may indicate that addicted smokers were more focused on completing the tasks than other groups, perhaps in order to smoke as soon as possible. Alternatively the findings may reflect that addicted smokers were aware they needed to concentrate in order to compensate.

All smokers became slower at encoding new information on the categoric search task in withdrawal. This is concordant with the findings of Snyder et al. (1989) using a comparable task (two-letter search), who showed that reaction times significantly slowed following 24-hour abstinence. Conversely, present data show smokers' reaction times were accelerated by withdrawal in categoric search trials where either no distracter or a neutral distracter was present. Comparing these findings with Snyder et al. (1989) is problematic since many more detailed and specific variables were generated by the current task.

There was a trend for smokers' performance on the vigilance/RVIP task to be impaired by withdrawal. This is consistent with previous findings (Snyder et al. 1989; Heimstra, 1980), and demonstrates the concentration difficulties described in the tobacco withdrawal syndrome. Snyder et al. (1989) used a serial subtraction/addiction task to test vigilance, and found that smokers' accuracy and response time was adversely affected by withdrawal.

Addicted and non-addicted smokers demonstrated few clear differences in terms of cognitive response to withdrawal. There was a trend for addicted smokers to show more accelerated response times than non-addicted smokers in categoric search trials where either no distracter or a neutral distracter was present. This result is difficult to explain, and contrasts with the findings of Shiffman et al. (1995), who showed that dependent smokers response times become slower in withdrawal on mathematics and logic tasks, whereas chippers response times are unaffected. Although non-significant, there was a trend that the vigilance of addicted smokers was more impaired than that of non-addicted smokers following withdrawal. Although vigilance/RVIP was not investigated explicitly by Shiffman et al. (1995), this finding would be expected if the principles demonstrated by their tasks generalised to other aspects of cognitive performance requiring attention and/or concentration.

Withdrawal had few effects on measures of smokers' mood. Post-test Anxiety was increased by 24-hour abstinence in the addicted smokers group. This increase was not found in the non-addicted smokers or non-smokers. Anxiety is a symptom of the tobacco withdrawal syndrome described in DSM-IV, and current findings parallel

those of previous research. Hughes & Hatukami (1986) found that abstinent smokers self-reported higher levels of anxiety than when they were non-deprived. Current findings are also broadly concordant with Shiffman et al. (1995), who showed that chippers "mood disturbance" was unaltered by withdrawal, but that dependent smokers "mood disturbance" was increased. Their "mood disturbance" factor featured several items that could be described as measuring anxiety. It is theoretically possible that addicted smokers are inherently more anxious than non-addicted smokers (discussed in Chapter 5) even prior to the onset of smoking, and these differences may re-emerge following abstinence. It is interesting that post-test and not pre-test Anxiety was affected by abstinence; perhaps addicted smokers felt their cognitive performance had been significantly worsened by withdrawal and were anxious primarily for that reason.

Tobacco-withdrawn smokers' cognitive performance was generally enhanced by 45 minutes of *ad libitum* smoking. Non-smokers simple reaction times were greatly increased in the third (Reinstated) session, whereas both smoking groups (although also increased) were much less decelerated/slowed. The non-smoker finding could be explained in terms of fatigue, with nicotine potentially demonstrating some protective efficacy against fatigue or boredom effects in the smokers. Similar results were yielded by the categoric search task, where non-smokers became slower encoding new information in their third session whilst all smokers became faster following reinstatement. This was the only specific cognitive performance variable that was shown to be both impaired by withdrawal and enhanced by reinstatement.

These findings are concordant with Snyder et al. (1989), who found that reaction times on all the cognitive tasks they examined were improved following tobacco reinstatement. This may reflect reductions in cholinergic function caused by abstinence, which are returned to baseline levels through reinstatement (e.g. Rezvani & Levin, 2001).

A trend was observed for non-addicted smokers reaction times to be more greatly accelerated following reinstatement than addicted smokers (and non-smokers) in categoric search trials with a neutral or absent distracter. These trials may be sensitive to learning effects since all subjects had progressively accelerated responses with each session. These findings suggest that non-addicted smokers derived greater cognitive facilitation from *ad libitum* smoking than addicted smokers on these task trials. Such a finding implies a direct effect of tobacco rather than a reversal of withdrawal effects.

Shiffman et al. (1995) did not examine differential reinstatement effects on cognitive performance of chippers and dependent smokers, but their results suggested that cognitive performance was improved by nicotine rather than worsened by withdrawal. However, Shiffman et al. (1995) did not show improvement of cognitive performance in chippers through smoking. The contrast with current findings may be due to the important differences in typology between "chippers" and "non-addicted smokers". "Chippers" are a stable non-dependent group whereas "non-addicted smokers" is a rather non-specific category. The latter group may contain individuals who are simply in transitional stages of smoking behaviour, and therefore may be in transitional levels of nicotine dependence.

Reinstatement was shown to have several effects on mood. Following *ad libitum* smoking, all smokers rated their post-test Alertness and (non-significantly) pre-test Alertness higher than when tobacco withdrawn. This finding is concordant with some previous research showing that acute smoking increases subjective arousal (Parrott, 1995b), although other studies have not replicated this effect (Shiffman et al. 2002). However, these previous studies did not have such an extensive withdrawal period prior to acute smoking, making direct comparison difficult. Reinstated smokers also experienced increases in post-test Hedonic Tone, demonstrating a marked improvement in mood following the removal of withdrawal.

Although direct comparison is problematic due to differences in methodology, these findings are broadly consistent with previous research where smokers rated themselves as happier and more sociable after smoking (Warburton, 1994). However, whether or not nicotine has a direct effect on mood and cognitive performance in humans or whether the majority or all its observed effects are a result of factors such as withdrawal reversal is a highly contentious area (e.g. Heishman, 1998; Waters & Sutton, 2000).

A trend was observed for addicted smokers to rate their post-test Anxiety lower following reinstatement, compared to small increases in non-addicted smokers and non-smokers. This is consistent with some previous research, although Kassel & Shiffman (1997) suggest that nicotine's effects on anxiety may be mediated through its cognitive effects. They reported that when smokers are presented with a benign distracter task, smoking might improve attentional focus. Therefore, these smokers

are less distracted by internal and external stimuli that may promote anxiety. This explanation does not adequately explain the findings of the current study, since only the addicted smokers experienced a reduction in Anxiety, whilst both smoking groups experienced modest improvements in cognitive task performance following reinstatement.

There are a number of potential issues that need addressing in this study. Greater numbers of subjects in the addicted smokers group would have added power to the statistical analyses. This could have resulted in several non-significant trends becoming significant effects, and may have elicited significant withdrawal effects on more variables. Secondly, although expired breath CO is a convenient way of testing whether a smoker has complied with the abstinence protocol, it is not infallible. Plasma nicotine or salivary cotinine levels with individual baseline measures would provide a more robust verification of abstinence.

Although this study examined a control group of non-smokers, future designs should look into administering nicotine to the non-smokers, or by having further groups of smoking participants who were not abstinent. This would have engendered further ethical and/or methodological issues, but may have clarified whether effects found in the Reinstatement condition were due to withdrawal reversal or any absolute effect of nicotine on mood or cognition. The 24-hour abstinence period was chosen since withdrawal symptoms are generally at their most severe at this time (Snyder et al. 1989). It would also be desirable to examine several different abstinence epochs; this

would allow analysis of the time-course of withdrawal, and any further differences therewith between addicted and non-addicted smokers.

The present study provides a profile of addicted and non-addicted smokers mood and cognitive responses to smoking abstinence and reinstatement. 24-hour tobacco withdrawal caused increased Anxiety in addicted smokers, but caused both positive and negative effects on cognitive performance; addicted smokers often performed better in the Withdrawn session. Reinstatement through 45 minutes *ad libitum* smoking increased Alertness and Hedonic Tone, while addicted smokers also demonstrated modest reductions in Anxiety. Non-addicted smokers derived apparent cognitive facilitation from nicotine on the categoric search task. The study suggests that addicted and non-addicted smokers are not well characterised by differences in their cognitive performance responses to nicotine withdrawal and reinstatement, although anxiety (a symptom of the tobacco withdrawal syndrome) may critically discriminate these groups.

Figure 3.1 **Graph showing different changes in post-test Anxiety scores following abstinence for the three groups.** Data are presented as mean change scores (n=75; non-smokers n=25, non-addicted smokers n=40, addicted smokers n=10), and error bars denote ± standard error of the mean (S.E.). Change scores were computed by subtracting Baseline (non-deprived) session scores from Withdrawn (24-hour abstinence) session scores. Addicted smokers differed to non-addicted smokers ($p<.05$).

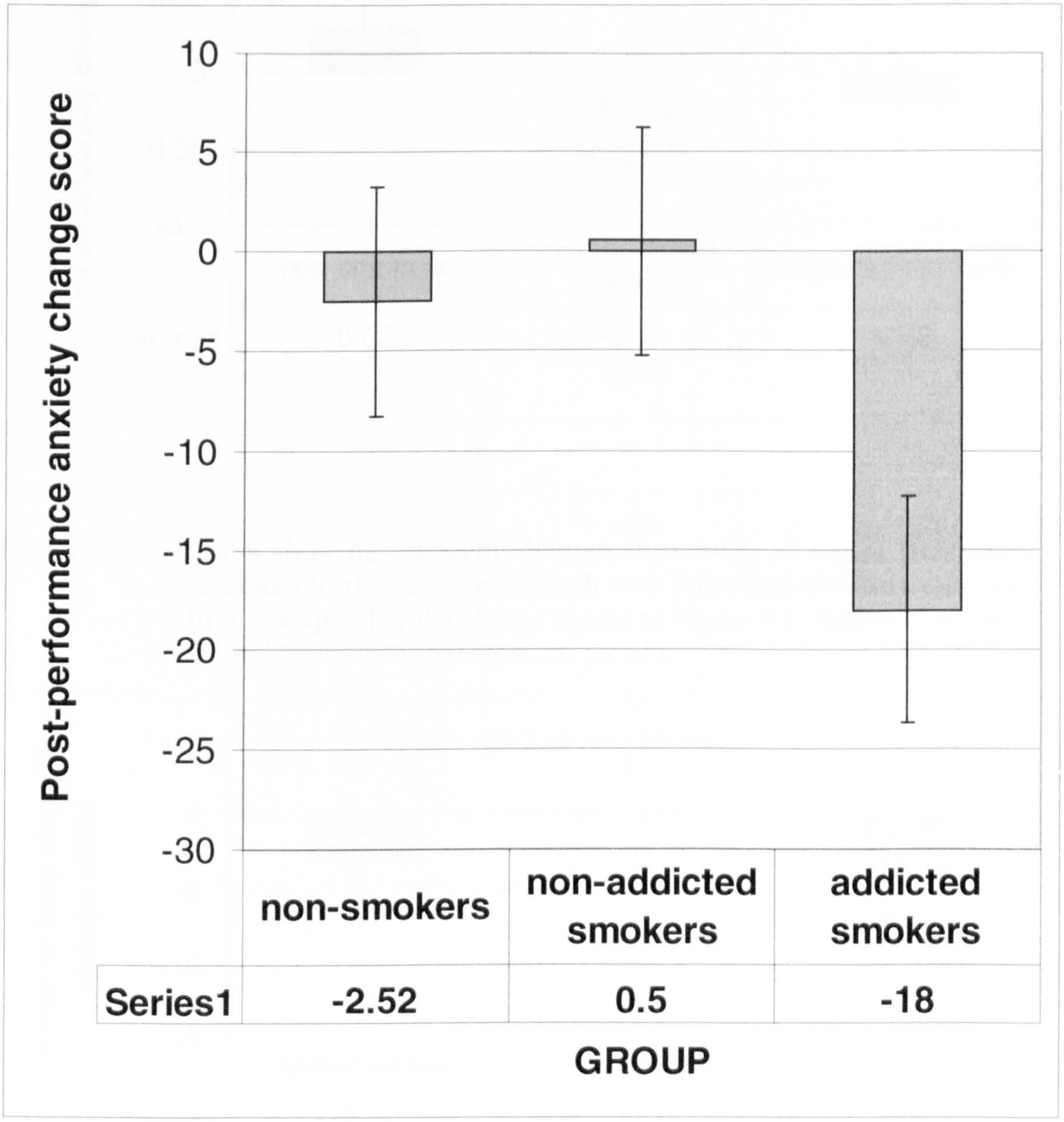


Figure 3.2 **Graph showing different changes in accuracy responding to targets presented alone or with asterisks in the focused attention task following abstinence for the three groups.** (For details see legend to Figure 3.1. Non-addicted smokers differed to non-smokers, $p<.05$).

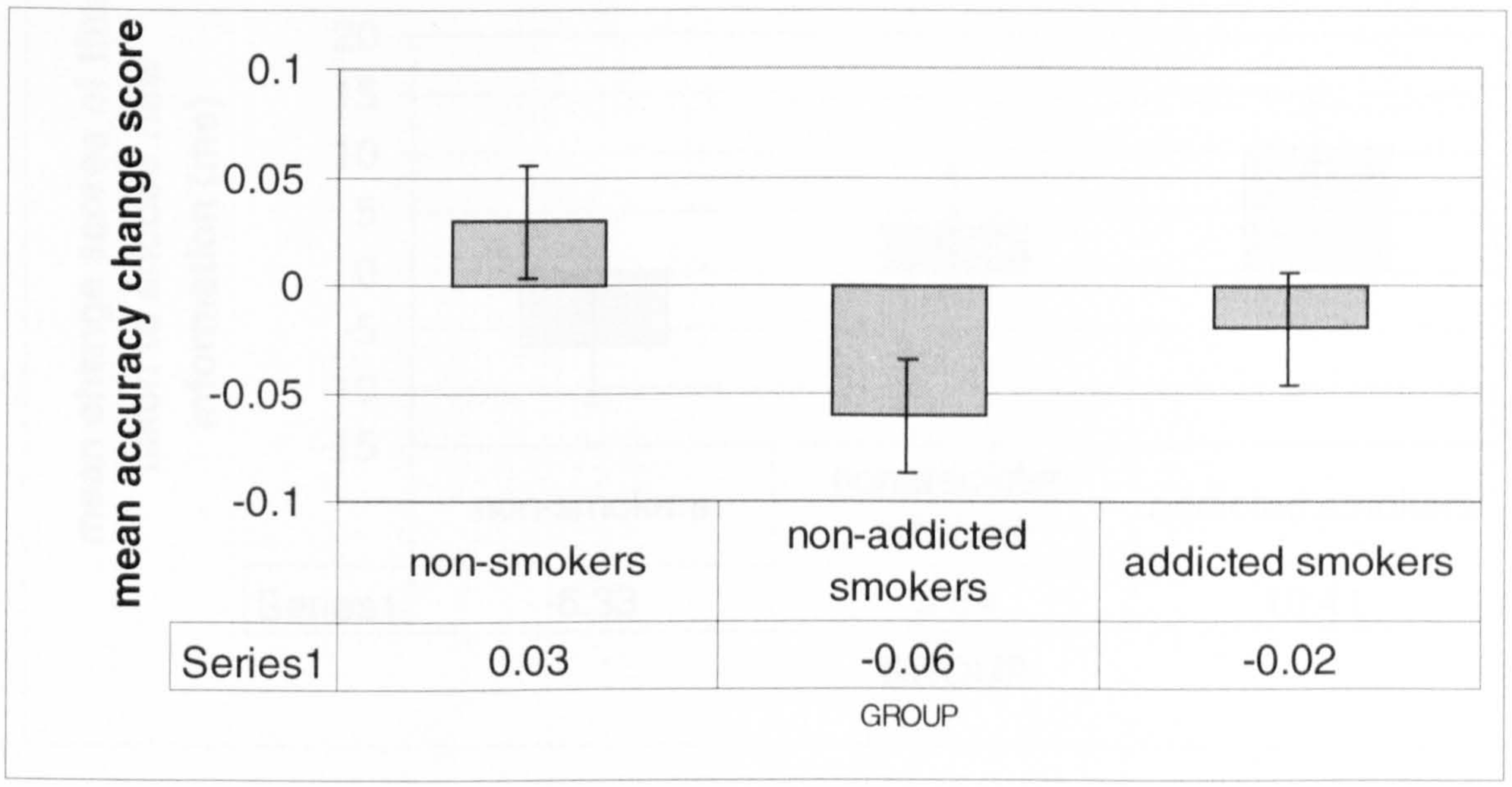


Figure 3.3 **Graph showing different changes in number of lapses (responses >1000ms) in the categoric search task following abstinence for the three groups.** (For details see legend to Figure 3.1. Addicted smokers differed to non-addicted smokers, $p<.01$).

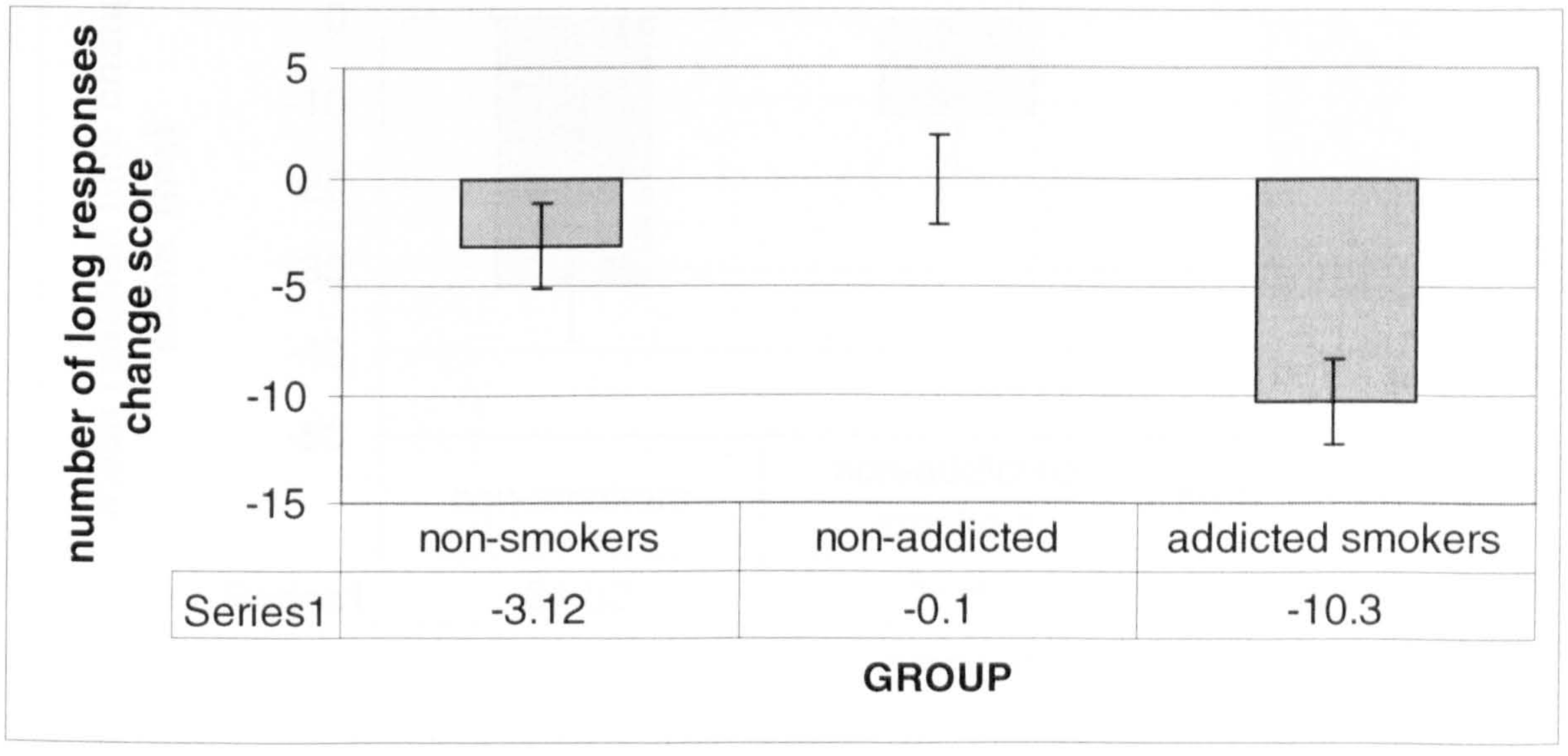


Figure 3.4 Graph showing different changes in speed of encoding new information in the categoric search task following abstinence for the three groups. (For details see legend to Figure 3.1).

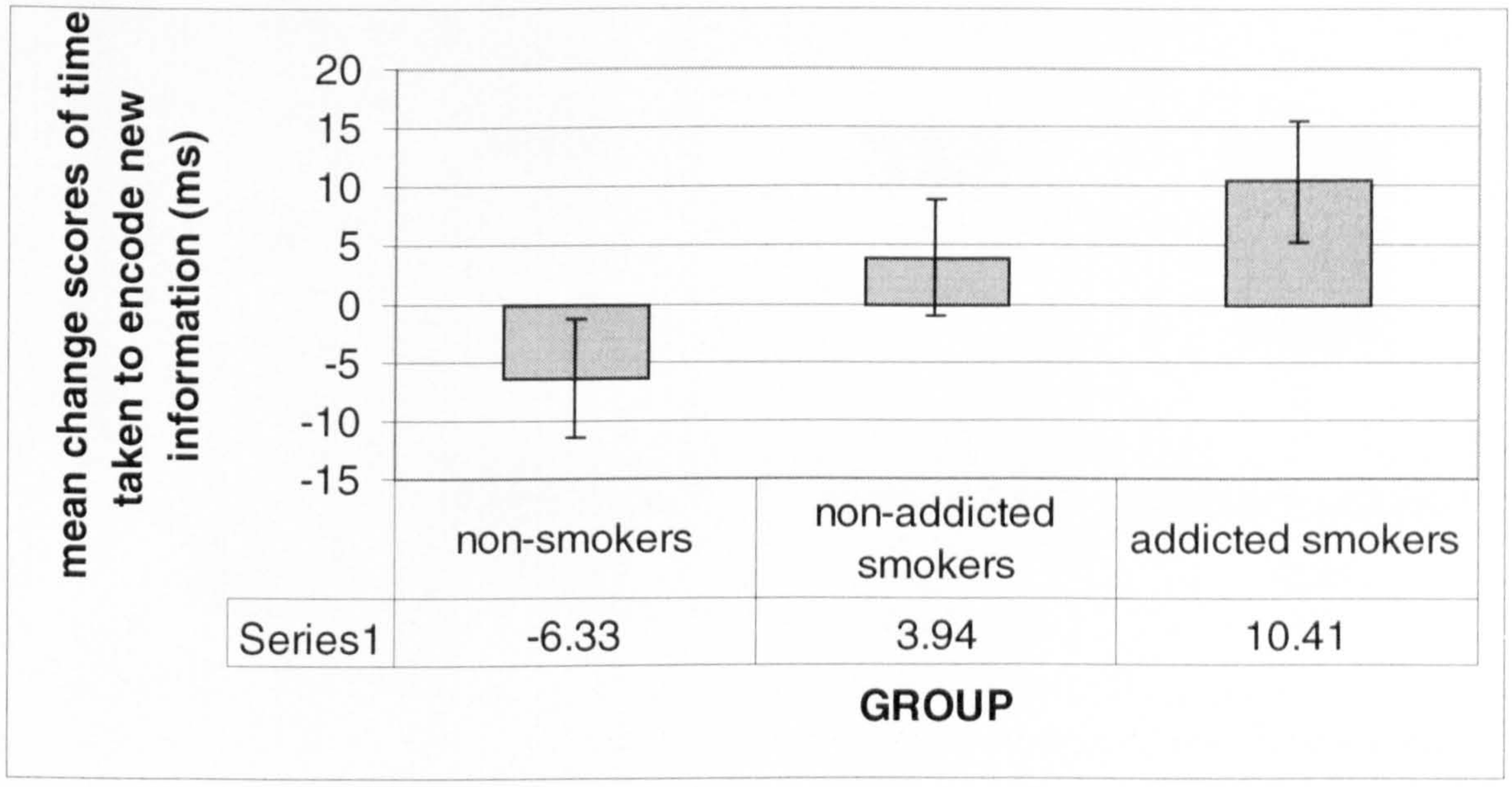


Figure 3.5 Graph showing different changes in reaction time responding to targets presented alone or with asterisks in the categoric search task following abstinence for the three groups. (For details see legend to Figure 3.1. Non-addicted smokers differed from non-smokers, $p<.05$).

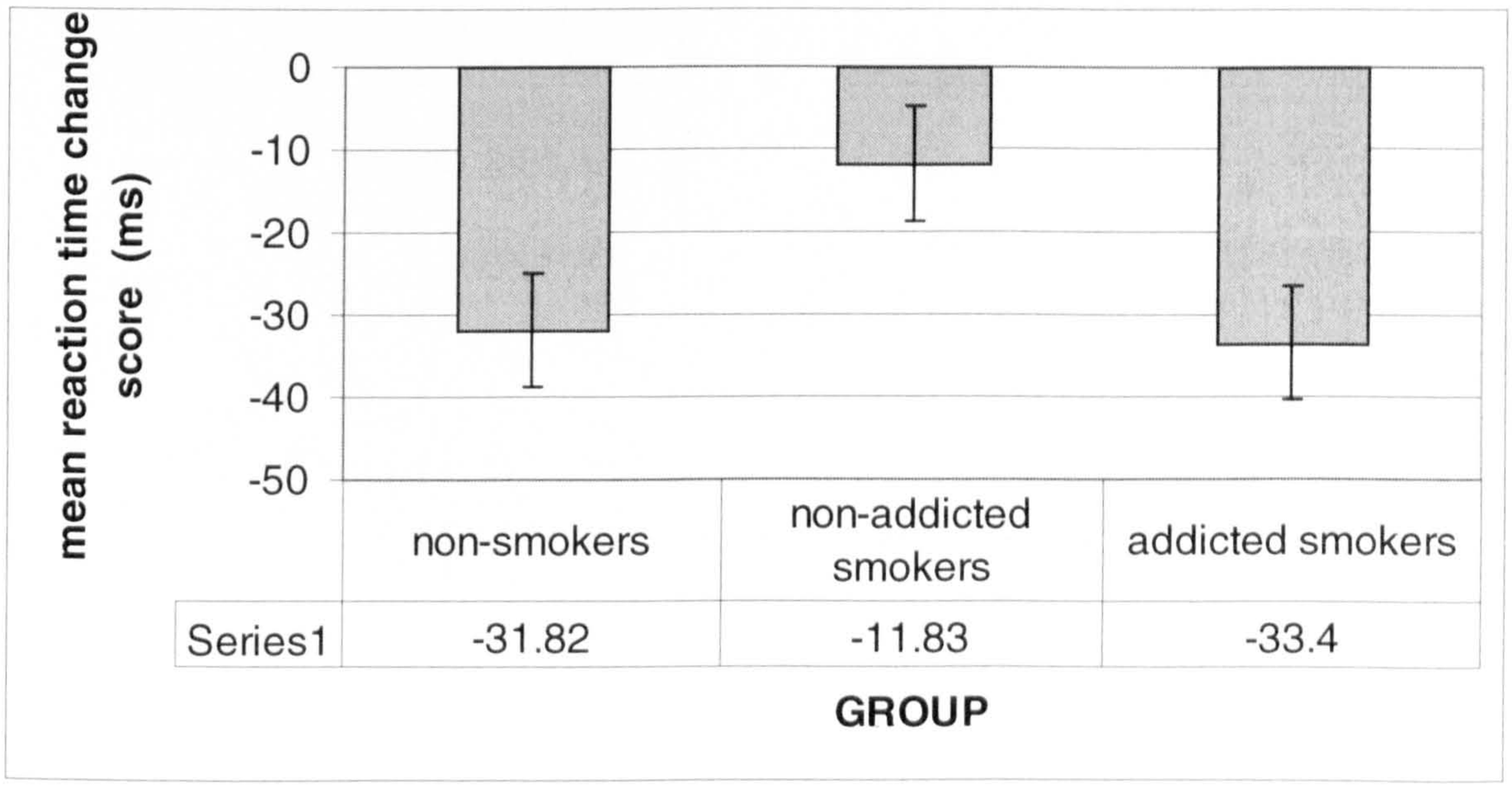


Figure 3.6 **Graph showing different changes in 'number of hits' on the repeated digits vigilance/RVIP task following abstinence for the three groups.** (For details see legend to Figure 3.1)

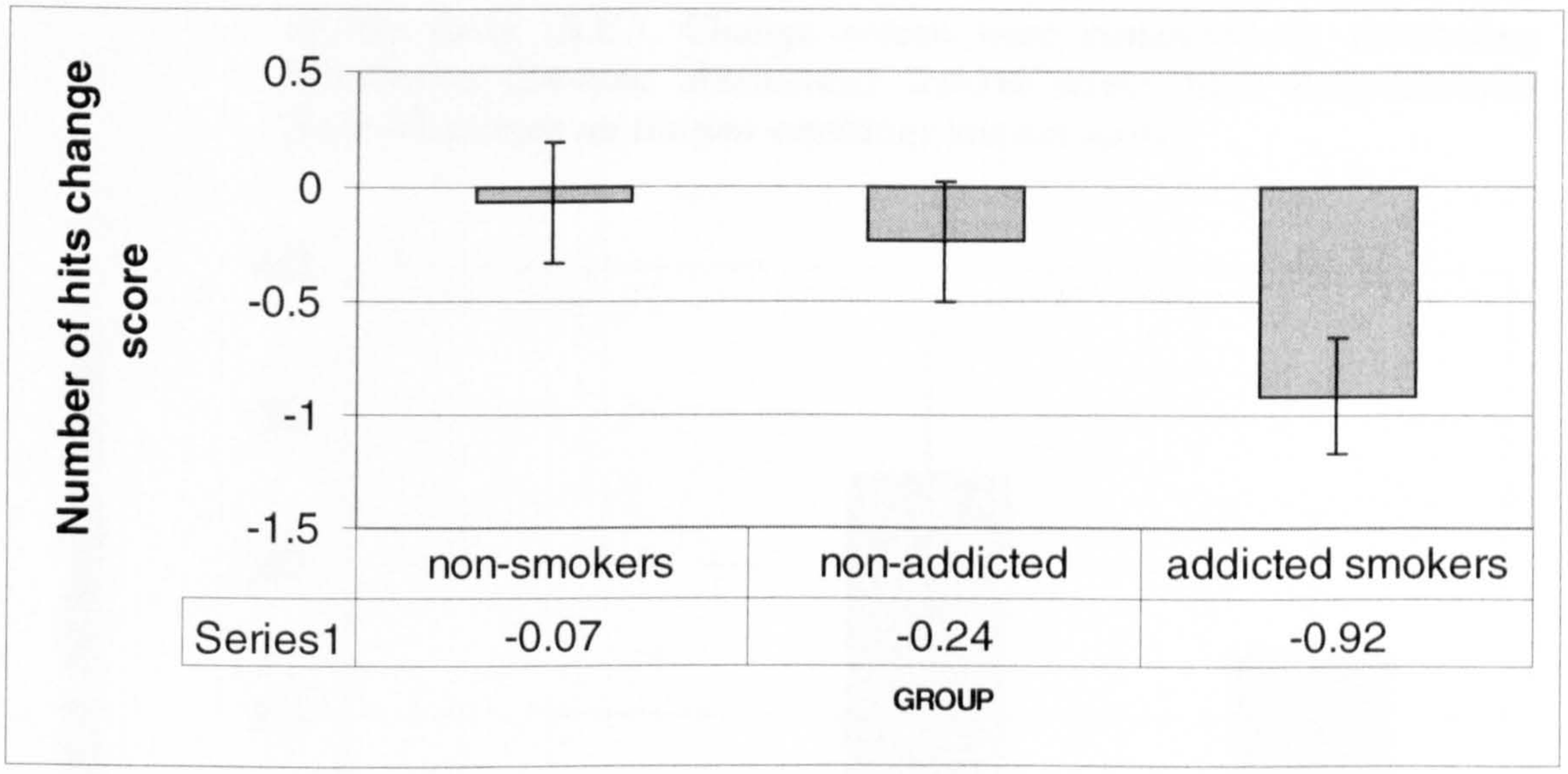


Figure 3.7 **Graph showing different changes in pre-test Alertness scores following reinstatement for the three groups.** Data are presented as mean change scores (n=75; non-smokers n=25, non-addicted smokers n=40, addicted smokers n=10), and error bars denote ± standard error of the mean (S.E.). Change scores were computed by subtracting Withdrawn (24-hour abstinence) session scores from Reinstatement (post-45-minute *ad libitum* smoking) session scores.

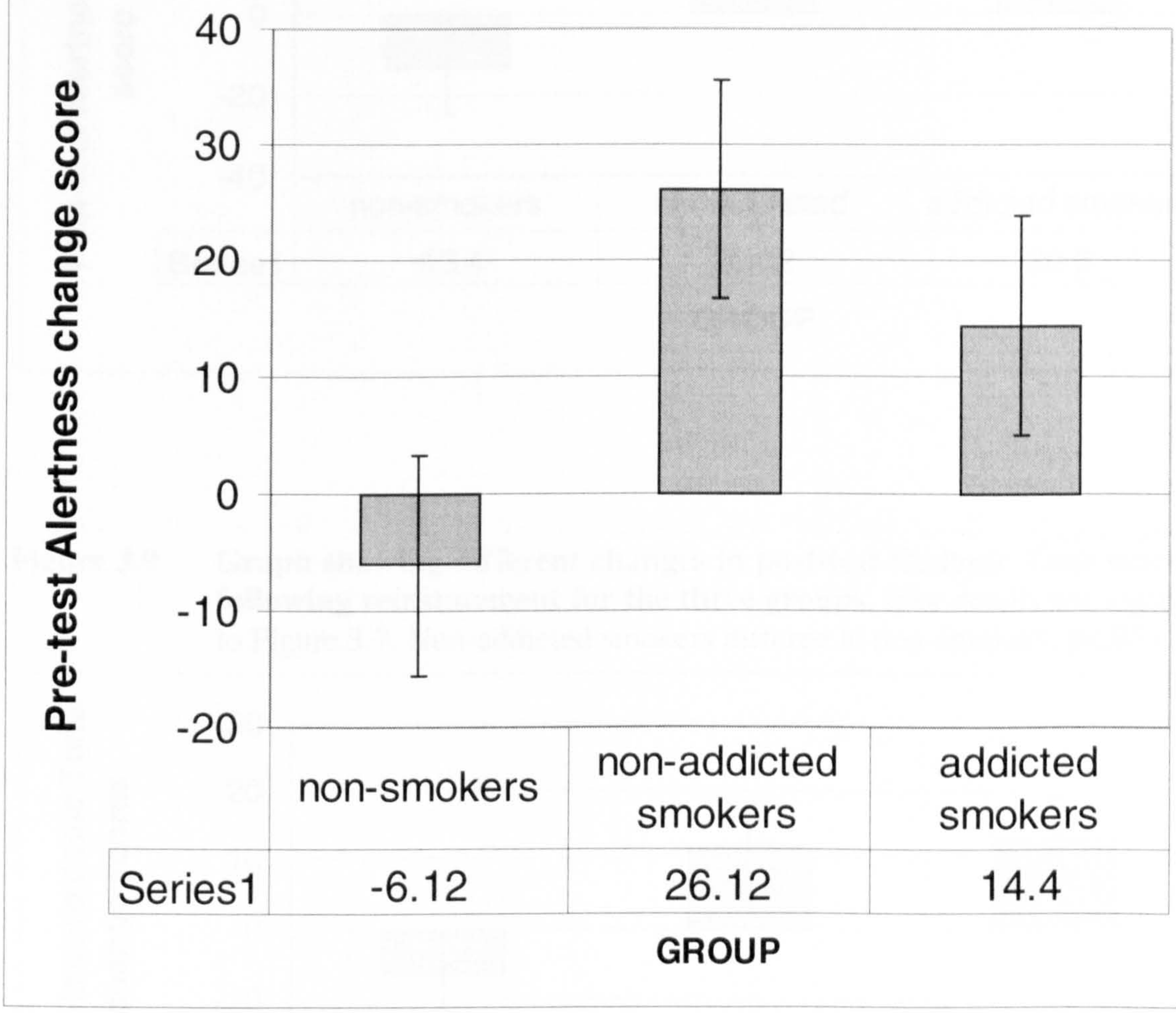


Figure 3.8 **Graph showing different changes in post-test Alertness scores following reinstatement for the three groups.** (For details see legend to Figure 3.7. Non-addicted smokers differed to non-smokers, p<.01).

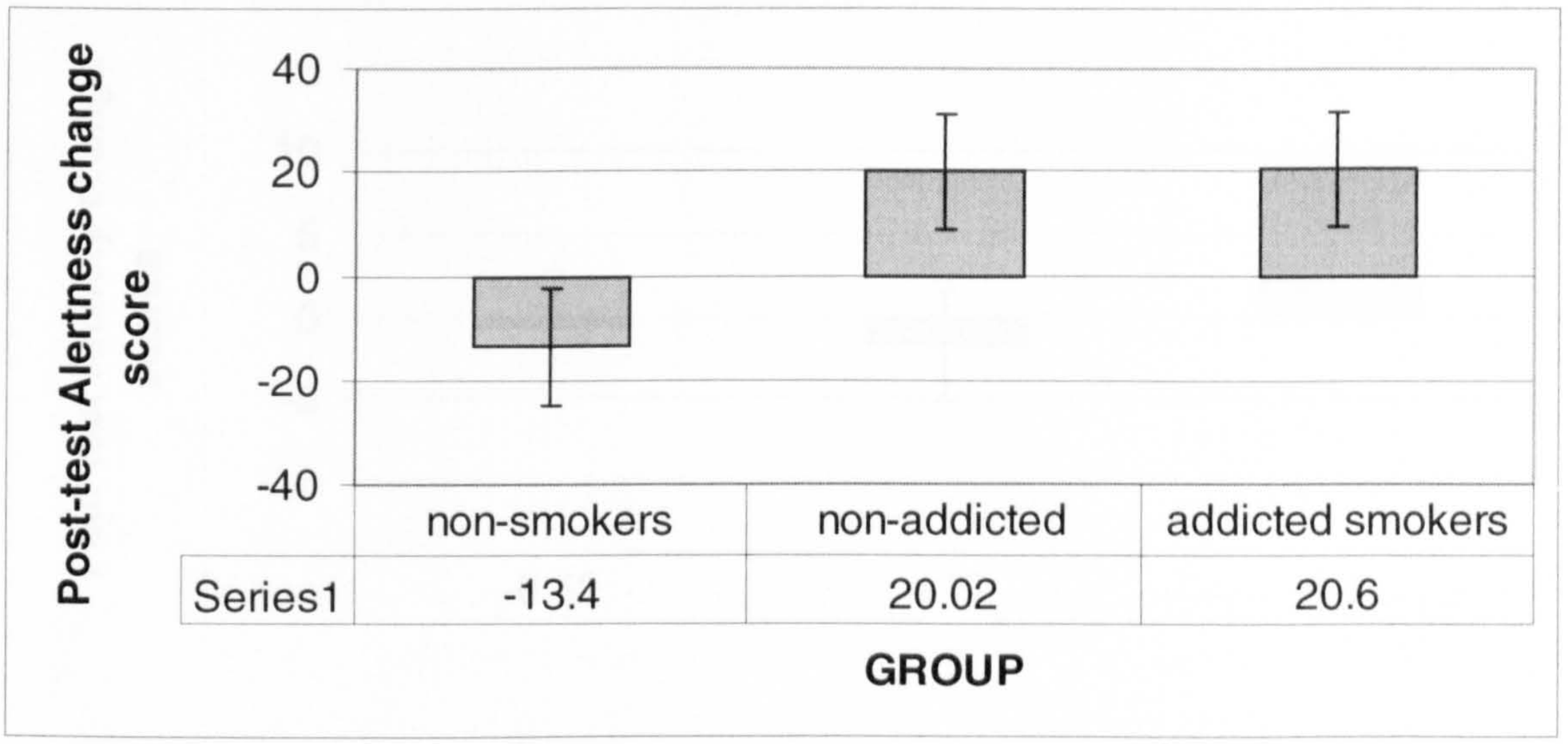


Figure 3.9 **Graph showing different changes in post-test Hedonic Tone scores following reinstatement for the three groups.** (For details see legend to Figure 3.7. Non-addicted smokers differed to non-smokers, p<.05).

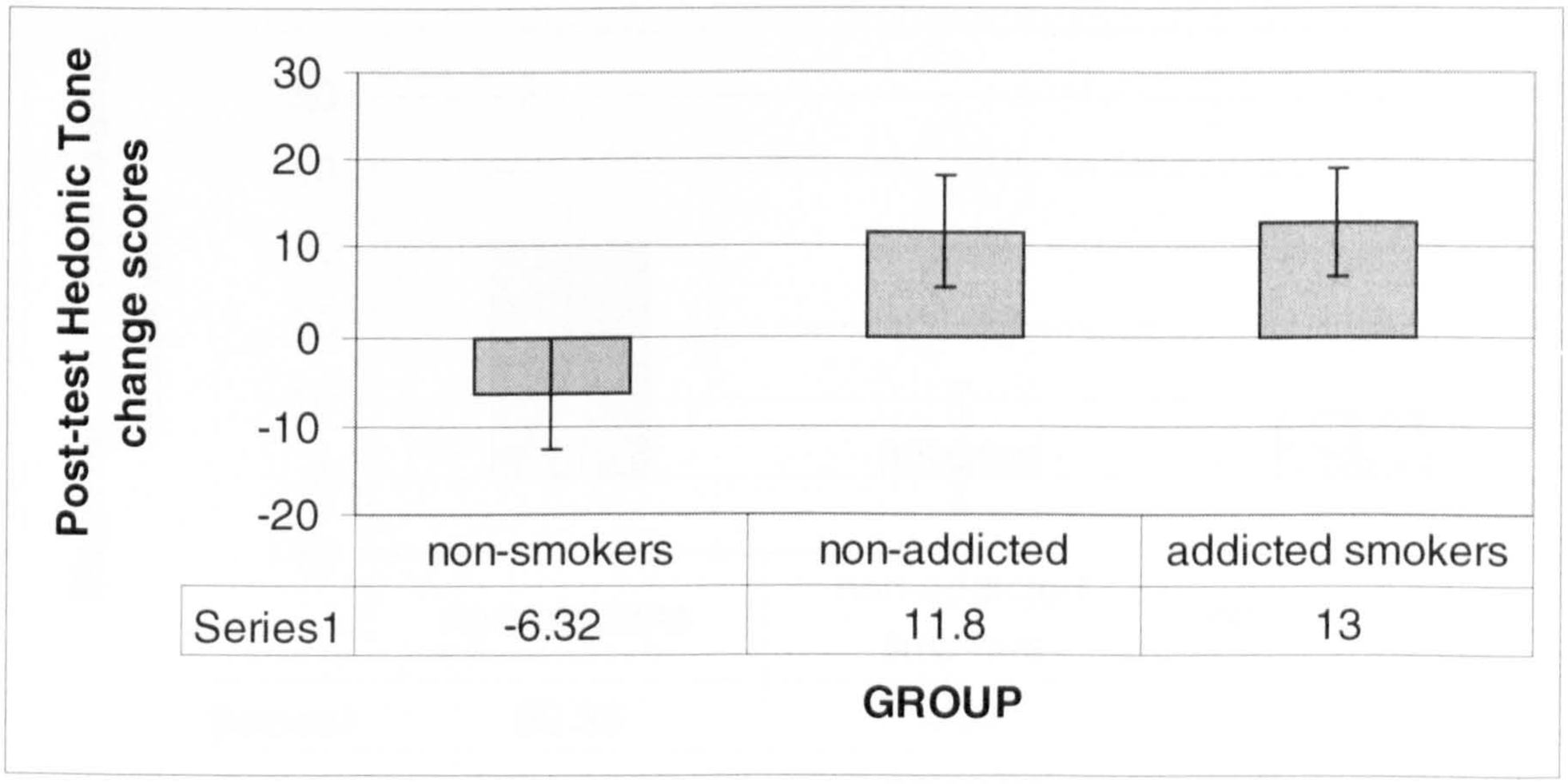


Figure 3.10 Graph showing different changes in post-test Anxiety scores following reinstatement for the three groups. (For details see legend to Figure 3.7).

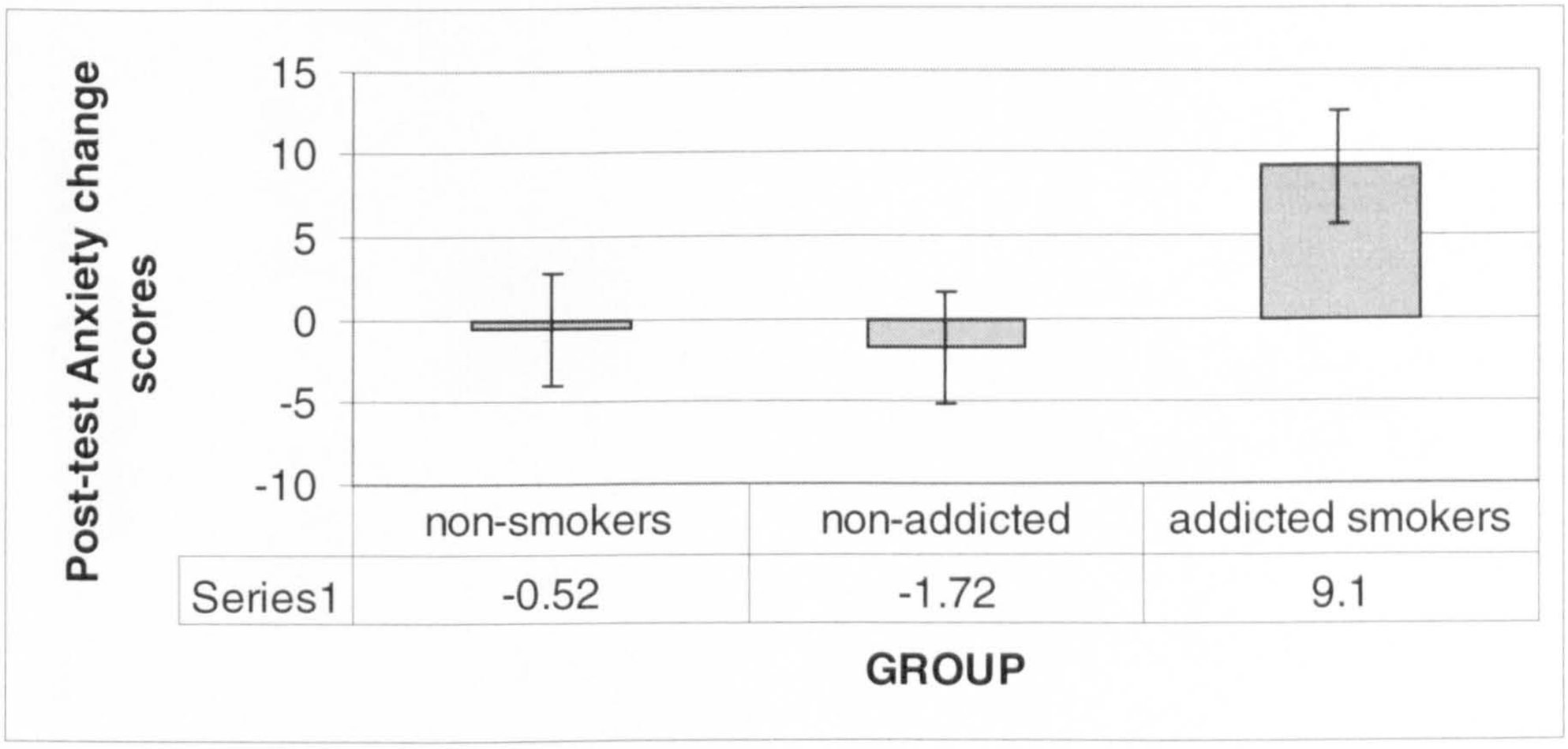


Figure 3.11 Graph showing different changes in mean total reaction time in the simple reaction time task following reinstatement for the three groups. (For details see legend to Figure 3.7. Non-addicted smokers differed to non-smokers, $p<.01$).

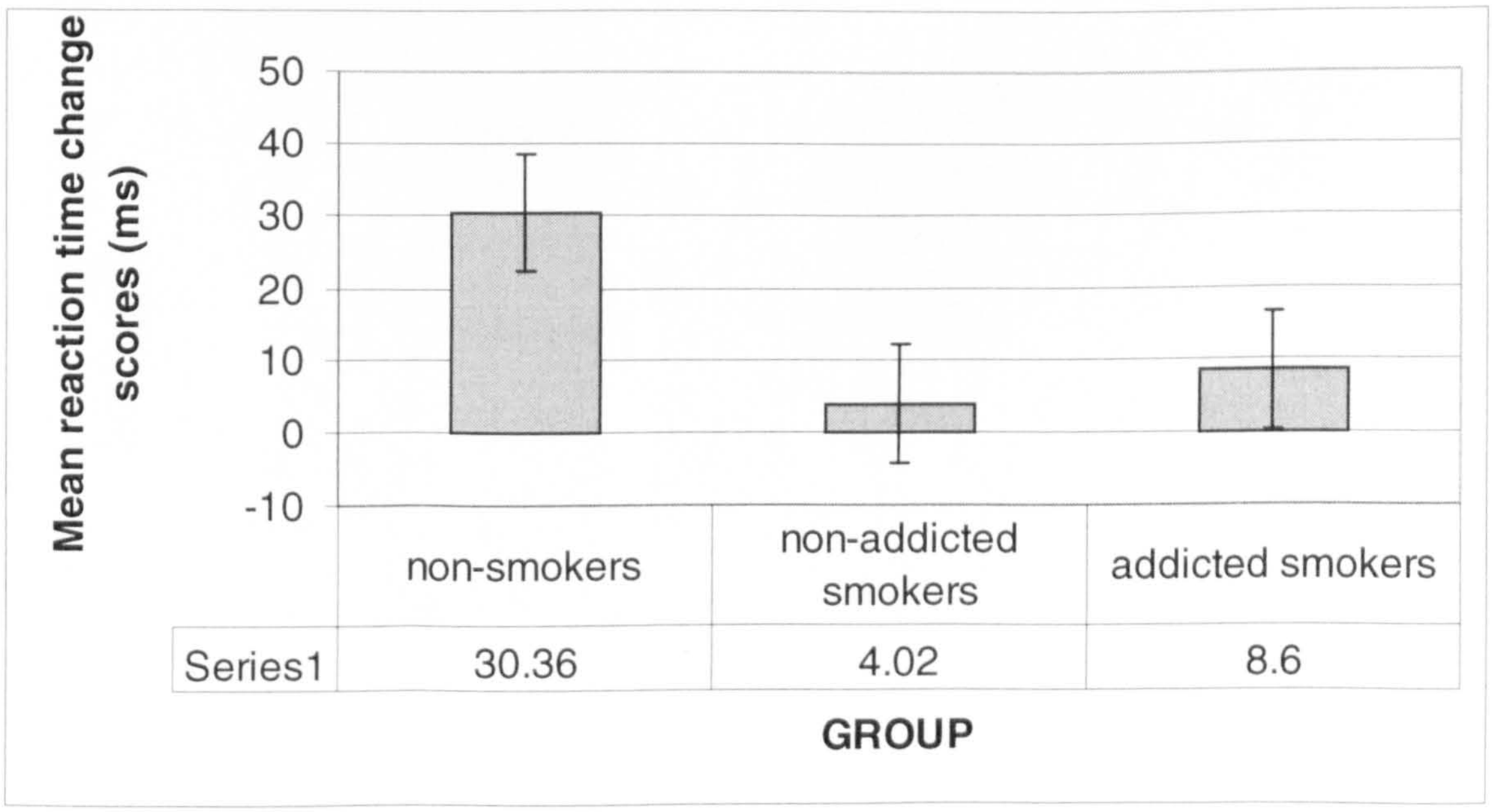


Figure 3.12 Graph showing different changes in speed of encoding new information in the categoric search task following reinstatement for the three groups. (For details see legend to Figure 3.7. Non-addicted smokers differed from non-smokers, p<.01).

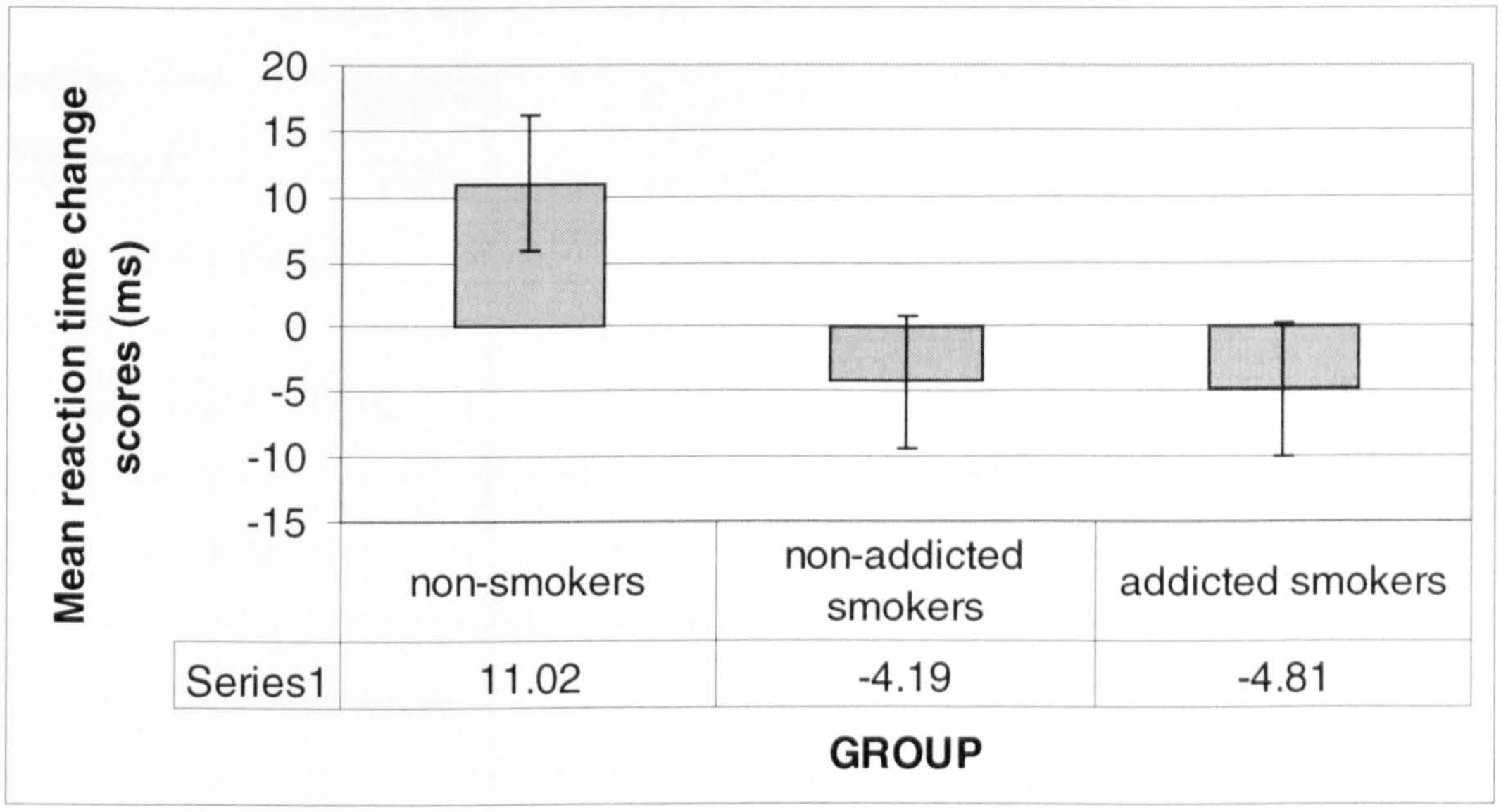


Figure 3.13 Graph showing different changes in speed of encoding new information in the categoric search task following reinstatement for the three groups. (For details see legend to Figure 3.7).

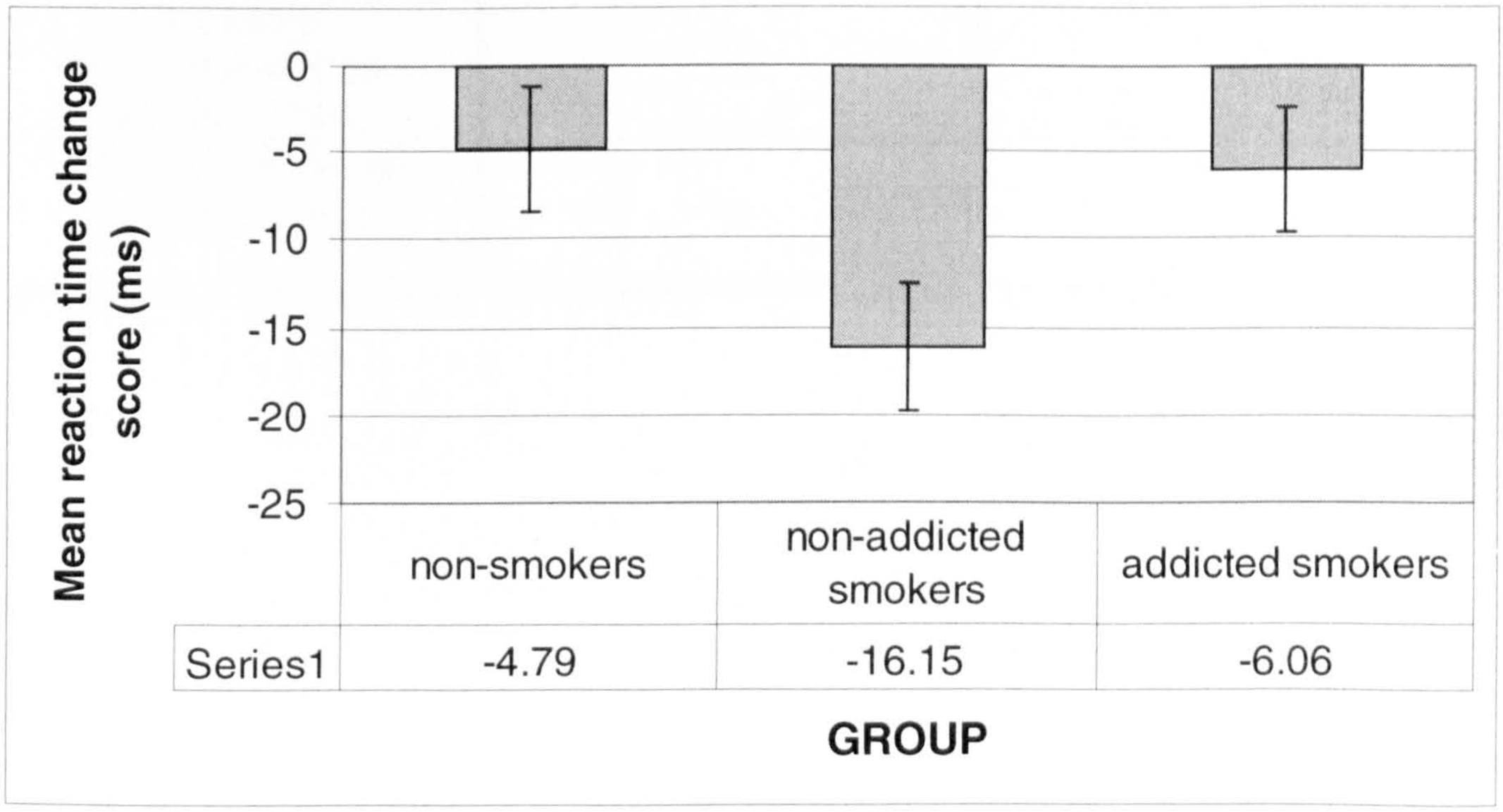


Table 3.1 **Summary of changes (relative to controls) in the mood and cognitive performance battery from the Baseline (non-deprived) to Withdrawn (24-hour abstinence) session in the smoking groups.** ↑=increase (or improvement), ↓=decrease (or decrement), ↑↓=some variables improved, others impaired, →=no change.

GROUP / MEASURE	NON-ADDICTED SMOKERS	ADDICTED SMOKERS
ALERTNESS	→	→
HEDONIC TONE	→	→
ANXIETY	→	↑
S.R.T. PERFORMANCE	→	→
FOCUSED ATTENTION PERFORMANCE	↓	↓
CATEGORIC SEARCH PERFORMANCE	↑↓	↑↓
5-CHOICE PSYCHOMOTOR PERFORMANCE	→	→
VIGILANCE / RVIP PERFORMANCE	→	↓

Table 3.2 **Summary of changes (relative to controls) in the mood and cognitive performance battery from the Withdrawn (24-hour abstinence) to Reinstated (post-45-minute *ad libitum* smoking) session in the smoking groups.** ↑=increase (or improvement), ↑↑=many variables improved, ↓=decrease (or decrement), →=no change. *Although SRT performance was impaired for smokers following reinstatement, the increases in reaction times were less than those for non-smokers, suggesting an anti-fatiguing effect of smoking.

GROUP / MEASURE	NON-ADDICTED SMOKERS	ADDICTED SMOKERS
ALERTNESS	↑	↑
HEDONIC TONE	↑	↑
ANXIETY	→	↓
S.R.T. PERFORMANCE	→*	→*
FOCUSED ATTENTION PERFORMANCE	→	→
CATEGORIC SEARCH PERFORMANCE	↑↑	↑
5-CHOICE PSYCHOMOTOR PERFORMANCE	→	→
VIGILANCE / RVIP PERFORMANCE	→	→

Chapter 4 – Dopamine receptor genetics, novelty-seeking personality types and smoking behaviour

4.1 Introduction

Smoking induces feelings of pleasure in those who are regular tobacco users, as most drugs subject to abuse increase hedonic tone. The nicotine in tobacco smoke is believed to be responsible for these effects. Dopamine, a major neurotransmitter of the central nervous system, is thought to be involved in the mesolimbic reward pathway (Wise & Rompre, 1989; Koob, 1992; Di Chiara, 1999). Nicotinic receptors have been identified on the dopaminergic cell bodies, and stimulation of these receptors by nicotine has been shown to cause an increase in release of dopamine in the nucleus accumbens (Pontieri et al, 1996). This structure is an integral part of the ascending mesolimbic system.

Increasing evidence suggests that polymorphisms of the dopaminergic system genes may be linked to susceptibility to a variety of conditions including alcoholism (Blum et al. 1990), polysubstance abuse (Smith et al. 1992), cocaine addiction (Noble et al. 1993) and pathological gambling (Comings et al. 1996b). Whilst environmental factors may be important determinants of smoking, the results of association, family and twin studies suggest that initiation and maintenance of smoking also involves hereditary factors (Hughes et al. 1986; Heath et al. 1995; Carmelli et al. 1992).

Due to the likely involvement of the mesolimbic dopamine system in nicotine addiction, several studies have examined dopamine receptor polymorphisms in relation to this condition. Studies looking at Caucasian populations in the United

States have shown a relationship between either the DRD2*A1 or the *B1 allele and genetic predisposition to smoking behaviour (Noble et al. 1994; Comings et al. 1996a; Spitz et al. 1998), although this association was not confirmed in a United Kingdom population (Singleton et al. 1998). A study of Japanese found different results again, with smoking behaviour shown to be associated with DRD2*A2 (homozygous) genotype (Yoshida et al. 2001). Other studies have found no linkage between DRD2 and smoking (e.g. Bierut et al. 2000).

DRD3 receptor genetics have also been implicated in addictive behaviour, with associations demonstrated between homozygosity and both cocaine dependence (Comings et al. 1999) and opiate dependence (Duaux et al. 1998). To date, no studies have examined the association between DRD3 polymorphisms and smoking behaviour.

An association between smoking behaviour and the DRD4 exon III L allele polymorphism has been reported for an African-American population (Shields et al. 1998). This study found that after smoking cessation counselling, individuals with the L allele were much less likely to be abstinent at 2 months compared with subjects who were homozygous for the S allele. This association, however, was not found in Caucasian subjects. Shields et al. (1998) also report that subjects who had at least one L allele had higher risk of smoking, shorter time to first cigarette in the morning and earlier age at smoking initiation. Associations have also been found between the DRD4 L allele polymorphism and opiate dependence (Kotler et al. 1997; Li et al. 1997), suggesting that D4 receptor genetics may have some basic influence on addiction per se.

The dopamine system and smoking behaviour may be linked via inherited personality traits. Gray (1973) purported that personality traits reflect motivational systems that evolved to increase adaptation to classes of stimuli associated with positive and negative reinforcement. Personality questionnaires have been developed (e.g. Tri-dimensional Personality Questionnaire (TPQ) (Cloninger, 1987) and Temperament & Character Index (TCI) (Cloninger et al. 1993)) as tools to study the genetics of personality, and these have been widely used. These questionnaires draw on human and animal work to suggest that behaviour is mediated by certain neurotransmitters, which underlie three basic heritable dimensions.

The temperament dimension 'Novelty Seeking' (NS) draws on aspects of impulsiveness, curiosity (or exploratory behaviour) and disorderliness, and is believed to reflect dopaminergic function. Impulsivity (a sub-scale of NS) perhaps represents the strongest link to smoking behaviour. People with high levels of impulsivity are thought to be more likely to experiment with psychoactive drugs and possibly become regular users (Johnson et al. 1993; Logue, 1995). Various studies report higher levels of impulsivity in smokers than non-smokers (Williams, 1973; Golding et al. 1983; Zuckerman et al. 1990; Jenks, 1992; Mitchell, 1999).

There is strong evidence of an association between the DRD4 L allele and Cloninger's NS personality trait (e.g. Ebstein et al. 1996; Benjamin et al. 1996). Since smokers showed higher NS rates than the general population (e.g. Pomerleau et al. 1992; Zuckerman et al. 1990), it is likely that the L allele is associated with smoking, concordant with Shields et al.'s (1998) findings in African-Americans.

The current study investigated the inter-relationship between personality traits, DRD2, D3 and D4 genetic polymorphisms and smoking behaviour.

Three experimental hypotheses were tested:

I. that addicted smokers will be more likely than non-addicted smokers to possess the *A1 polymorphism for DRD2 *Taq*IA, and possess homozygous DRD3 *Bal*I genes. Furthermore, all smokers will be more likely to possess the DRD2*A1 and homozygous DRD3 genotypes than non-smokers.

II. that there is an association between Novelty Seeking and DRD4 exon III polymorphism, with those subjects scoring higher on the Novelty Seeking scale more likely to possess the L allele of this gene.

III. that addicted smokers will be more likely to possess the DRD4 L allele compared with non-addicted smokers, and that together high Novelty Seeking and possession of L allele will be associated with higher Addiction Index scores.

4.2 Method

4.2.1 Design

This was a between subjects comparison of three groups (non-smokers, addicted smokers and non-addicted smokers) using Cloninger's (1993) Temperament & Character Inventory and genotyping polymorphisms of D2 (DRD2 *Taq*IA), D3 (DRD3 *Bal*I) and D4 (DRD4 exon III) dopamine receptors.

4.2.2 Subjects

Subjects (N=77) participated as part of the mood and cognitive performance study presented in Chapter 3. The participants were categorised as non-smokers (n=25), addicted smokers (n=10) and non-addicted smokers (n=42). Two participants provided a DNA sample, but quit the study prior to completion. A full description of the subject sample and recruitment information is included in Chapters 2 and 3.

4.2.3 Materials

Cloninger's (1993) Temperament & Character Inventory (TCI) was used to measure Novelty Seeking. This is a 240-item true-false self-report questionnaire, taking approximately 45 minutes to complete. It was administered as a pen-and-paper questionnaire, with written instructions. Seven dimensions of personality were derived: the original three Tridimensional Personality Questionnaire scales (or "temperaments") of Novelty Seeking, Harm Avoidance and Reward Dependence (Cloninger et al. 1994) and a fourth dimension, Persistence. Three "character" dimensions were also derived: Self-directedness, Cooperativeness and Self-transcendence. The TCI also measured 25 more specific traits that define the temperament and character dimensions: these are presented as sub-scales of each. The full questionnaire can be seen in Appendix XI.

DNA was collected using buccal DNA collection kits. Each of these comprised of a barcode-labelled stoppered plastic test tube containing 10ml saline and a pack of 10 buccal stick swabs. Each swab was used and placed into the solution: when all 10 were completed the tube was sealed and stored at room temperature, out of direct light.

4.2.4 Procedure

All participants gave informed written consent, and were notified which genes would be examined. The consent form is included in Appendix XII.

Once all samples for all subjects were collected, these were sent to Dr David Ball at The Social Genetic and Developmental Psychiatry Research Centre laboratory at the Institute of Psychiatry, Denmark Hill, London. Here the DNA was extracted from the cheek cell material contained in the buccal swabs and the dopamine receptor polymorphisms of the participants' genotypes were characterised. A laboratory technician blind to subjects' identities carried out PCR amplification.

Buccal cells collected in the oral swabs were pelleted and lysed in 3.0ml of cell lysis solution. The crude DNA extract was deproteinated with 300µg of proteinase K for 2 hours at 55°C, and an additional 300µg of proteinase K were added for overnight digestion. RNA was digested by adding 60µg of Rnase A for 30 minutes at 37°C. Protein from the DNA extract was removed with 1.0ml of protein precipitation solution after centrifuging at 2000 x *g* for 10 minutes, washed in 70% ethanol, briefly air-dried, and resuspended in TLE (10 mM Tris-HCl, 0.1 mM EDTA, pH 7.4) buffer.

DRD2 analysis

DRD2*A genotypes were determined by means of PCR using sense (5'-CCGTCGACCCTTCCTGAGTGTCATCA-3') and antisense (5'-CCGTCGACGGC TGGCCAAGTTGTCTA-3') oligonucleotide primers (Noble et al. 1994). The resulting PCR products were digested with *Taq*I, followed by electrophoretic separation on 3% agarose gels.

DRD3 analysis

*Bal*I restriction fragment length polymorphism at the first exon was performed according to the method described by Lannfelt et al. (1992). The primers used for DNA amplification were 5'-GCTCTATCTCCAACTCTCACA-3' and 5'-AAGTCTACTCACCTCCAGGTA-3'. PCR reaction contained 150ng genomic DNA, 2 U Taq polymerase, 1 x Taq polymerase buffer, 0.5μM each primer, 100μM dATP, dCTP, dGTP, dTTP, 0.01% gelatin in a total volume of 50μl. Samples were heated to 95°C for 6 minutes to denature DNA. Thirty-five cycles were performed according to the following steps: 92°C for 1 minute, 56°C for 1 minute, 72°C for 1 minute, followed by a final extension of 7 minutes.

The PCR products were subsequently digested with *Msc*I restriction enzyme (isoschizomer of *Bal*I) for 2 hours and the digested products were analysed on a 3% agarose gel. This polymorphism revealed a 2 allele system, allele 1 was 304 bp in length, allele 2 consisted of two fragments of 206 and 98 bp in length. Two constant bands at 111 and 47 bp were present.

DRD4 analysis

The DNA region containing the 48 base pair repeat in exon III of the DRD4 gene was amplified using primers D4-3 (5'-GCGACTACGTGGTCTACTCG-3') and D4-12 (5'-GGTCTGCGGTGGAGTCTG-3'). PCR conditions were chosen according to the method by Lichter et al. (1993) with the exception that the initial denaturing step was extended to 5 minutes. PCR fragments were separated in 15% polyacrylamide gels (acrylamide:bisacrylamide = 49:1) containing 1 x TBE and visualised by silver staining (Budowle et al. 1991).

4.3. Results

4.3.1 DRD2*A *Taq*I Polymorphism

The DNA encoding for DRD2*A presents 2 alleles. These genes are either homozygous (both alleles being the same) or heterozygous (different alleles). The sample (N=73, DRD2 data unobtainable for 4 subjects) contained all three possible genotypes: A1/A1 (n=5, 6.8%), A1/A2 (n=24, 32.9%) and A2/A2 (n=44, 60.3%), see Figure 4.1. Thus 29 subjects (39.7%) possessed the A1 allele (see Figure 4.2). The difference in distribution of the DRD2*A genotype among addicted smokers, non-addicted smokers and non-smokers (see Table 4.1) was non-significant as determined by the chi-square test (Fisher Exact used due to low observed cell counts). It was observed that participants who smoked (regardless of addiction status) were more likely to have the A2/A2 genotype, although this was not statistically significant (Table 4.2, Figure 4.3).

4.3.2 DRD3 *Bal*I Polymorphism

The DNA encoding for DRD3 *Bal*I presents 2 alleles. These genes are either homozygous or heterozygous. The sample (N=71, DRD3 data unobtainable for 6 subjects) contained all three possible genotypes: 1-1 (n=29, 40.8%), 1-2 (n=35, 49.3%) and 2-2 (n=7, 9.9%) (Figure 4.4). Thus 36 subjects (50.7%) possessed homozygous DRD3 *Bal*I genes. The difference in distribution of the DRD3 *Bal*I genotypes among addicted smokers, non-addicted smokers and non-smokers (see Table 4.3) was non-significant as determined by the Pearson chi-square test. Results were non-significant both when the sample was clustered by the three genotypes and when homozygous subjects were compared with heterozygous subjects. It was observed that participants who smoked (regardless of addiction status) were more

likely to possess a homozygous DRD3 *Bal*I genotype, although this was not statistically significant (Table 4.4, Figure 4.5).

4.3.3 DRD4 exon III Polymorphism and Novelty Seeking

The DNA encoding for DRD4 exon III presents with 2 alleles. These genes are either homozygous or heterozygous. The sample (N=77) contained 10 different DRD4 genotypes (Figure 4.6), whereby the most common alleles are the D4.2, D4.4 and D4.7 polymorphisms (Table 4.5). Subjects homozygous for the D4.4 alleles represent the largest portion of the variations, followed by those heterozygous for D4.4 and D4.7 alleles. Subjects were divided into two groups: L allele (D4.7 or D4.8) present (n=24, 31% of sample), and L allele absent (n=53, 69% of sample) (Figure 4.7).

Five (50%) of the addicted smokers possessed the L allele for DRD4, compared with only twelve (29%) of the non-addicted smokers and seven (28%) of the non-smokers (Figure 4.8). The association between possession of DRD4 L allele and smoking group was not significant when examined using Pearson chi-square.

The relationship between scores of Novelty Seeking (NS) and its sub-scales and the presence of the L allele of DRD4 was investigated. NS and its component subscale means were higher when the L allele was present (Table 4.6). Two subjects did not complete TCI questionnaires, hence the reduction in group sizes. The subjects possessing the L allele had significantly greater NS scores ($F\{1,73\}=4.26$, $p<.05$) than those lacking the L allele. Of the sub-scales, Impulsivity demonstrated significantly higher scores with the presence of L allele ($F\{1,73\}=5.74$, $p<.025$), and

Disorderliness showed a non-significant trend for the L allele present group to have higher scores (F{1,73}=3.42, p=.068).

Addicted smokers score higher on NS and all its sub-scales (particularly Impulsiveness) compared to non-addicted smokers, with non-smokers being lower than all smokers (see Table 4.7). Analyses of variance with Tukey post-hoc analyses were performed to examine the differences between the groups. Novelty Seeking was shown to differ according to smoking group (F{2,72}=7.97, p<.001). Both addicted smokers (p<.001) and non-addicted smokers (p<.025) had significantly higher NS scores than non-smokers.

Impulsiveness subscale was shown to differ according to smoking group (F{2,72}=7.98, p<.001). Both addicted smokers (p<.001) and non-addicted smokers (p<.025) had significantly higher Impulsiveness scores than non-smokers. There was also a trend for addicted smokers to have higher Impulsiveness scores than non-addicted smokers, which marginally failed to reach significance (p=.057) (Figures 4.9 and 4.10). Extravagance (F{2,72}=5.08, p<.01) and Disorderliness (F{2,72}=5.21, p<.01) were also both shown to differ according to smoking group; in both subscales both addicted (p<.025) and non-addicted (p<.05) smokers had higher scores than non-smokers.

4.4 Discussion

The results of this study demonstrated non-significant trends for associations between polymorphisms of D2, D3 or D4 dopamine receptors and smoking behaviour. Furthermore, significant relationships were found between the DRD4 L allele and NS

personality trait, with subjects possessing the L allele shown to have higher NS, particularly higher Impulsivity. It was also shown that NS scores differed between groups with different smoking behaviours. Addicted smokers and non-addicted smokers had significantly higher NS than non-smokers; again particularly in the Impulsivity subscale, but also shown in the Extravagance and Disorderliness subscales. A trend for addicted smokers to demonstrate higher Impulsivity than non-addicted smokers narrowly failed to reach significance. It is argued that DRD4 polymorphism is likely to be indirectly linked to smoking behaviour via novelty seeking personality traits.

No association was observed between the DRD2*A *Taq*I genotypes and smoking behaviour. This finding supports Bierut et al.'s (2000) study showing no linkage between DRD2*A polymorphism and smoking behaviour. The incidence distribution of the three DRD2*A genotypes was comparable with previous research (e.g. Spitz et al. 1998; Wu et al. 2000). The findings here do not replicate those suggesting DRD2*A1 allelic association with smoking found in several previous studies (e.g. Spitz et al. 1998), however there was a non-significant trend for subjects with the A2/A2 genotype to be current smokers, regardless of addiction status. This result supports findings of Yoshida et al. (2001), who showed an association between "ever-smokers" and the homozygous A2 genotype in Japanese subjects. This association in the current research may have become significant if a larger number of subjects had been genotyped. Most studies in this field being discussed analysed in excess of three hundred people, whereas the current study only genotyped seventy-seven.

There was also no significant association between homozygous DRD3 *Bal*I genotypes and smoking behaviour. Although no previous research has examined the association

between DRD3 polymorphisms and smoking behaviour, past studies have shown associations between homozygosity of the *Bal*I variant and opioid and cocaine dependence (Duaux et al. 1998; Comings et al. 1999). The incidence distribution of the three DRD3 *Bal*I genotypes was comparable with previous research (e.g. Duaux et al. 1998). The current research shows a slight trend for current smokers to be more likely to possess the homozygous genotype than the non-smokers. Given that susceptibility to drug addiction is polygenic and with major environmental factors (Cadoret et al. 1986), it has been suggested that individual genes rarely contribute more than 2% of the variance of a given trait (Comings et al. 1998). With these statistical levels, it further adds to the importance of having large samples when analysing genetic psychiatric data. If larger numbers had been tested in the current study, it is possible that *Bal*I homozygosity would have been significantly associated with smoking status.

DRD4 exon III polymorphisms were significantly related to Novelty Seeking personality trait scores, which is turn was highly associated with smoking status. The findings provide moderate support for the findings of Shields et al. (1998), who observed an association between possession of the L allele (D4.7 or D4.8) and smoking behaviour. The incidence of the various genotypes was consistent with previous research (Van Tol et al. 1992; Ebstein et al. 1996). The mean Novelty Seeking score for the sample was 23.5, which is higher than previous studies (e.g. Cloninger et al. 1993; Herbst et al. 2000; Richter et al. 1999). This may be a result of using a student sample rather than the general population samples used in earlier studies. Furthermore, two-thirds of the current sample were smokers (smokers normally comprise approximately one third of the population). Non-smokers mean NS (20.4) was closer to those previously reported.

The results show that those with the L-allele had significantly higher NS scores than those without the allele. This finding replicates the Ebstein et al. (1996) and Benjamin et al. (1996) studies. For example, Ebstein et al. (1996) found those who had the 7-repeat allele (D4.7) present had higher mean NS scores than those without the 7-repeat allele. It appears that Impulsiveness contributes critically to this difference, as the current results show it is the most significantly increased subscale associated with presence of the L allele. Previous studies have not examined the association between the NS subscales and DRD4 polymorphism.

Dopamine receptors expressed by the D4.7 or D4.8 alleles have a lower relative affinity for dopamine than those expressed by shorter alleles (Asghari et al. 1994). It may be that individuals with these alleles are self-medicating for a lower general dopaminergic function by behaving in such a way as to promote dopamine release. It is possible that individuals possessing the L-allele are prone to novelty seeking because they derive the most noticeable reward from activities that increase dopaminergic activity. Another possibility is that individuals are attempting to boost dopamine levels in a way to modulate affect.

The addicted smokers had higher mean scores of NS and all its subscales than the non-addicted smokers, although only the Impulsiveness subscale was statistically significantly different between the groups. These results are consistent with previous research showing that regular smokers are more impulsive than non-smokers (e.g. Carton et al. 1994; Mitchell, 1999). A number of theories could explain this finding. The lack of impulse control may mean that once smoking behaviour is initiated and patterns of drug use are developing, impulsive individuals may find restraint harder, thus escalating their use more quickly and developing tolerance. This could result in

rapid development of dependence. Alternatively, the sensitivity to nicotine's rewarding effects and impulsive behavioural tendencies could be related, or even simultaneous manifestations of a particular dopaminergic function profile.

The Exploratory sub-scale may be more salient to smoking initiation, which is not believed to be prone to genetic influence (Heath & Madden, 1995). This could explain why there is little difference between the addicted and non-addicted smokers on this factor. It is possible therefore that smoking behaviour is related to novelty seeking in a multi-factorial way, with smoking persistence mediated by Impulsiveness and smoking initiation mediated by Exploratory factors. These theories provide considerable scope for further research, requiring a detailed examination of the relationship between smoking behaviours and novelty seeking personality types.

Addicted smokers were statistically no more likely to possess the DRD4 L-allele than non-addicted smokers. However, in the addicted smokers group there are as many individuals with the L-allele as without. This is not the case in the non-addicted group, with only about a third possessing the L-allele. Although the DRD4 L-allele does not explain the variance between 'addicted' and 'non-addicted' based on the criteria used in this series of studies, the greater incidence of the L-allele in the 'addicted smokers' group may be important. An interesting associative triangle is emerging, comprising DRD4 exon III genotype, personality and tobacco dependence.

Susceptibility to nicotine dependence may be a direct result of D4.7/D4.8 receptor expression, as the resultant lowered dopamine affinity promotes behaviours that will stimulate dopamine release. Results obtained here suggest it may be that the observed relationship between DRD4 genotypes and smoking behaviour is indirect. Conceivably, the DRD4 genotype might well predict or determine novelty-seeking

personality traits (Ebstein et al. 1996; Benjamin et al. 1996). The impulsiveness element (measured in the NS trait) is a risk factor or source of predisposition for nicotine addiction (e.g. Mitchell, 1999). Clearly the relationship between dopamine and addiction needs considerable further investigation, in order to tease out specific relationships. It is argued from these results that possessing the L-allele genotype for DRD4 exon III is significantly associated, either directly or indirectly, with being both a novelty-seeker and a tobacco addict.

Caution is required drawing conclusions from this data due to the small number of addicted smokers in the sample. Power calculations demonstrate that there would need to be six more addicted smokers at this level of association to show a statistically significant effect. Furthermore, it is understood that the definition of addicted and non-addicted smoker is not definitive, and may have resulted in some subjects being incorrectly categorised. Caution is also required generalising these results due to the sampling method, although the sample was representative of a Caucasian student population.

In conclusion, these findings suggest a moderate role for dopamine receptor genetics in relation to smoking behaviour, although greater numbers of subjects may have elicited more significant results. DRD2*A *Taq*I and DRD3 *Bal*I polymorphisms have a limited, if any, role in nicotine addiction. DRD4 exon III polymorphisms may have a more salient influence on smoking behaviour, with L alleles (D4.7 and D4.8) shown to be associated with higher scores on Cloninger's (1993) Novelty Seeking. NS, particularly the Impulsiveness subscale, was higher in smokers than non-smokers, and highest in the addicted smokers. The results suggest that possession of DRD4 L allele indirectly increases an individual's susceptibility to nicotine dependence.

Figure 4.1 Graph showing DRD2*A *Taq*I genotype incidence of entire sample.

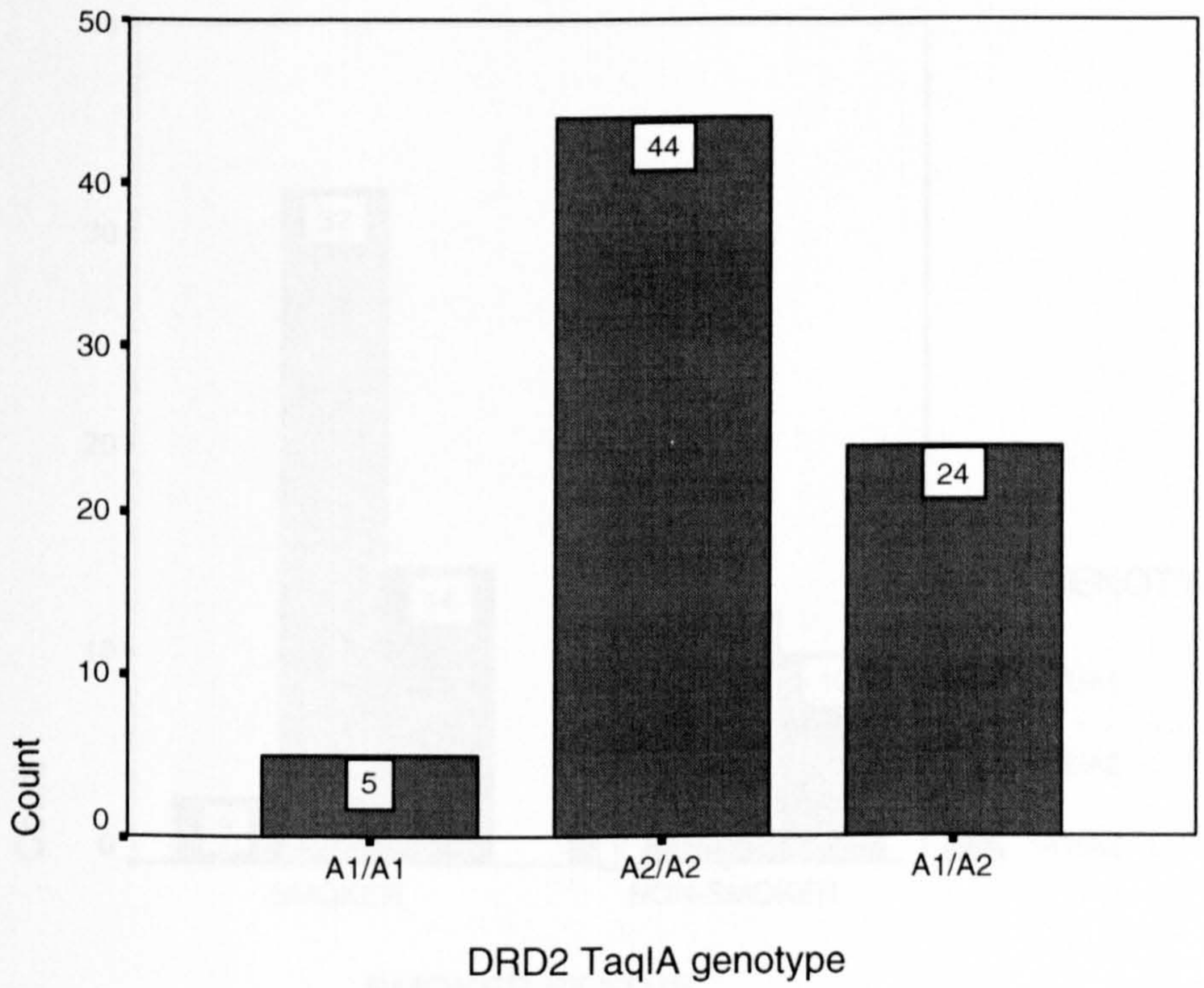


Figure 4.2 Graph showing incidence of DRD2*A1 *Taq*I allele of entire sample.

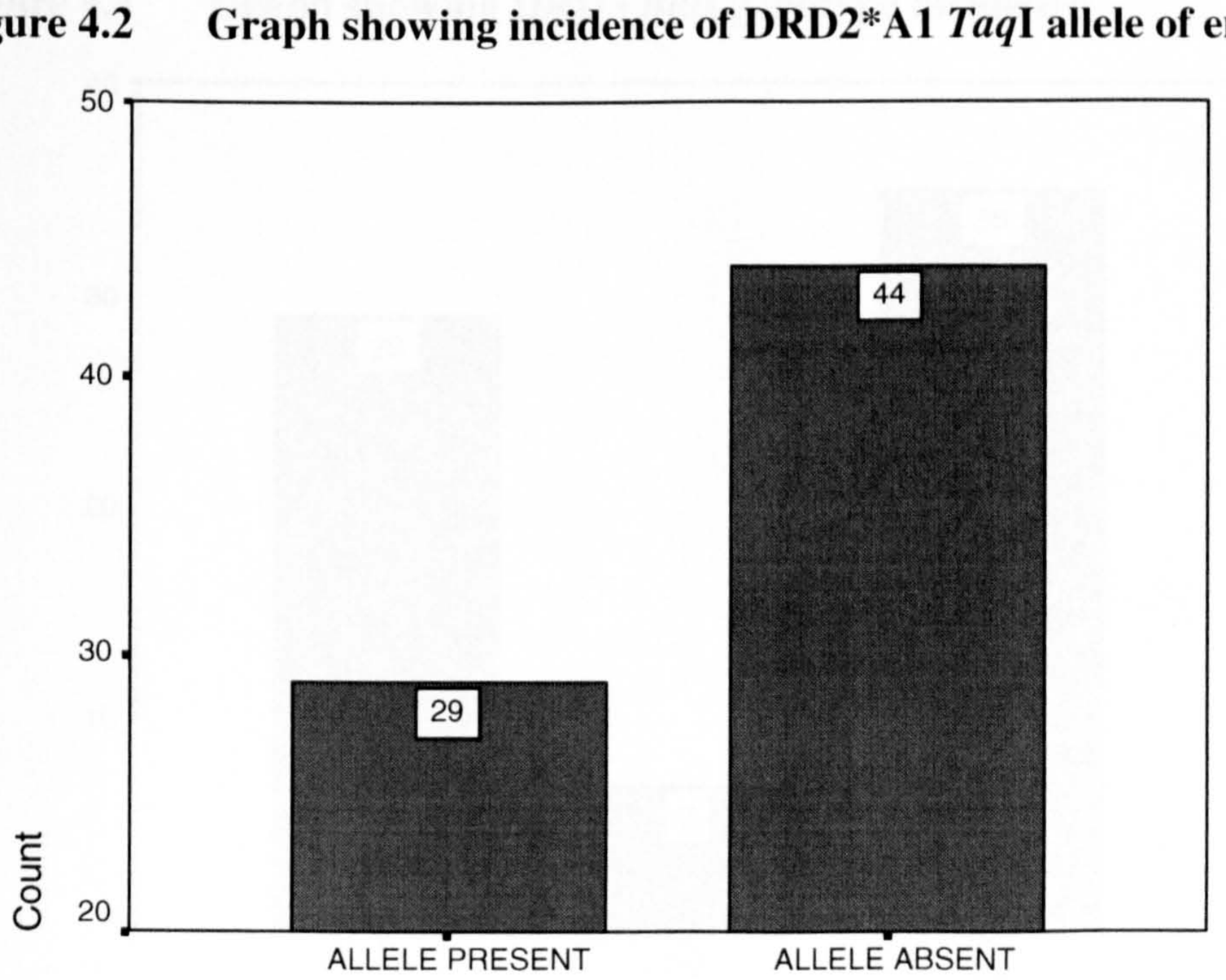


Figure 4.3 Graph showing distribution of DRD2*A *Taq*I genotypes between smokers and non-smokers.

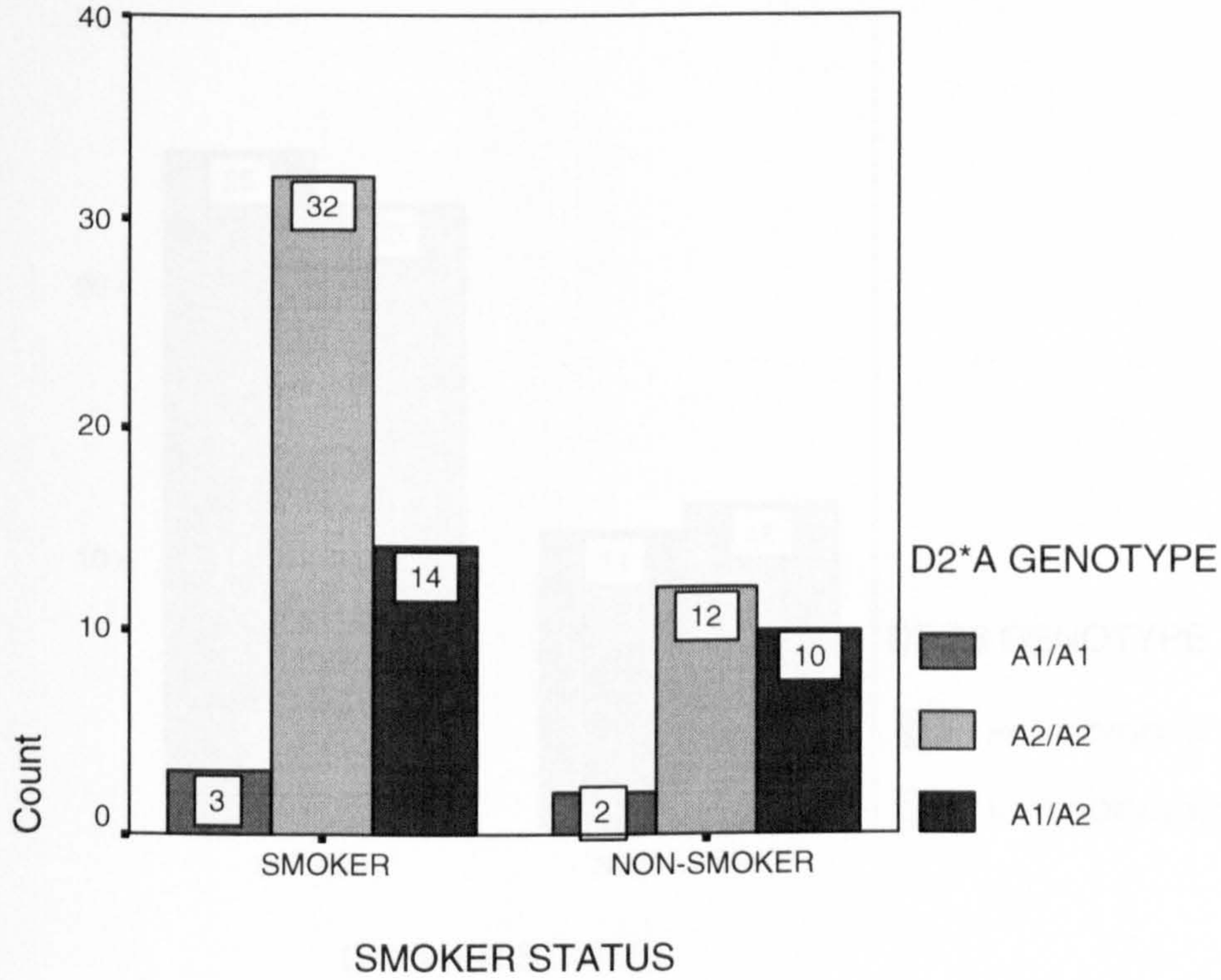


Figure 4.4 Graph showing DRD3 *Bal*I genotype incidence

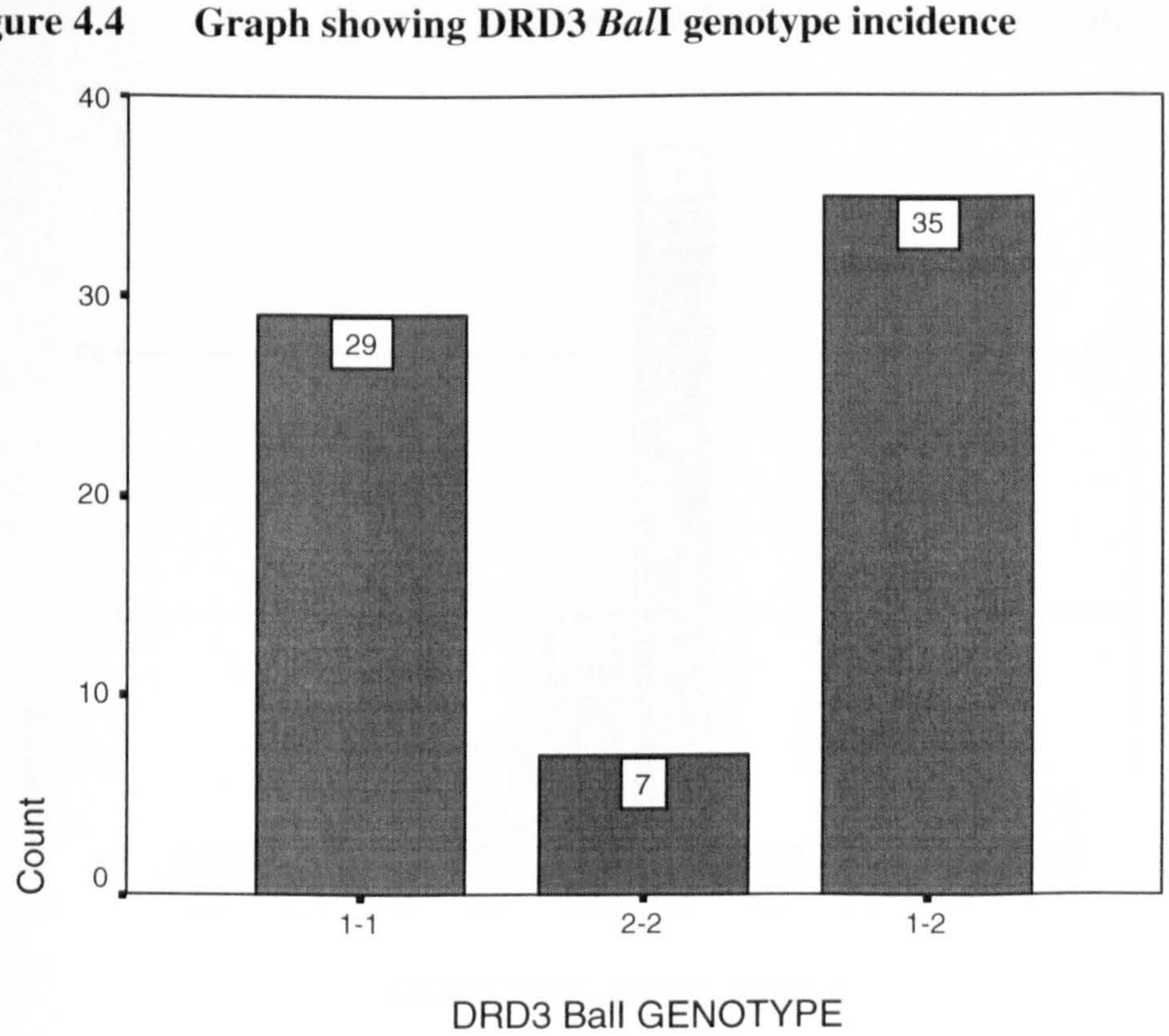


Figure 4.5 **Graph showing incidence of homozygous DRD3 *Bal*I genotype in smokers and non-smokers.**

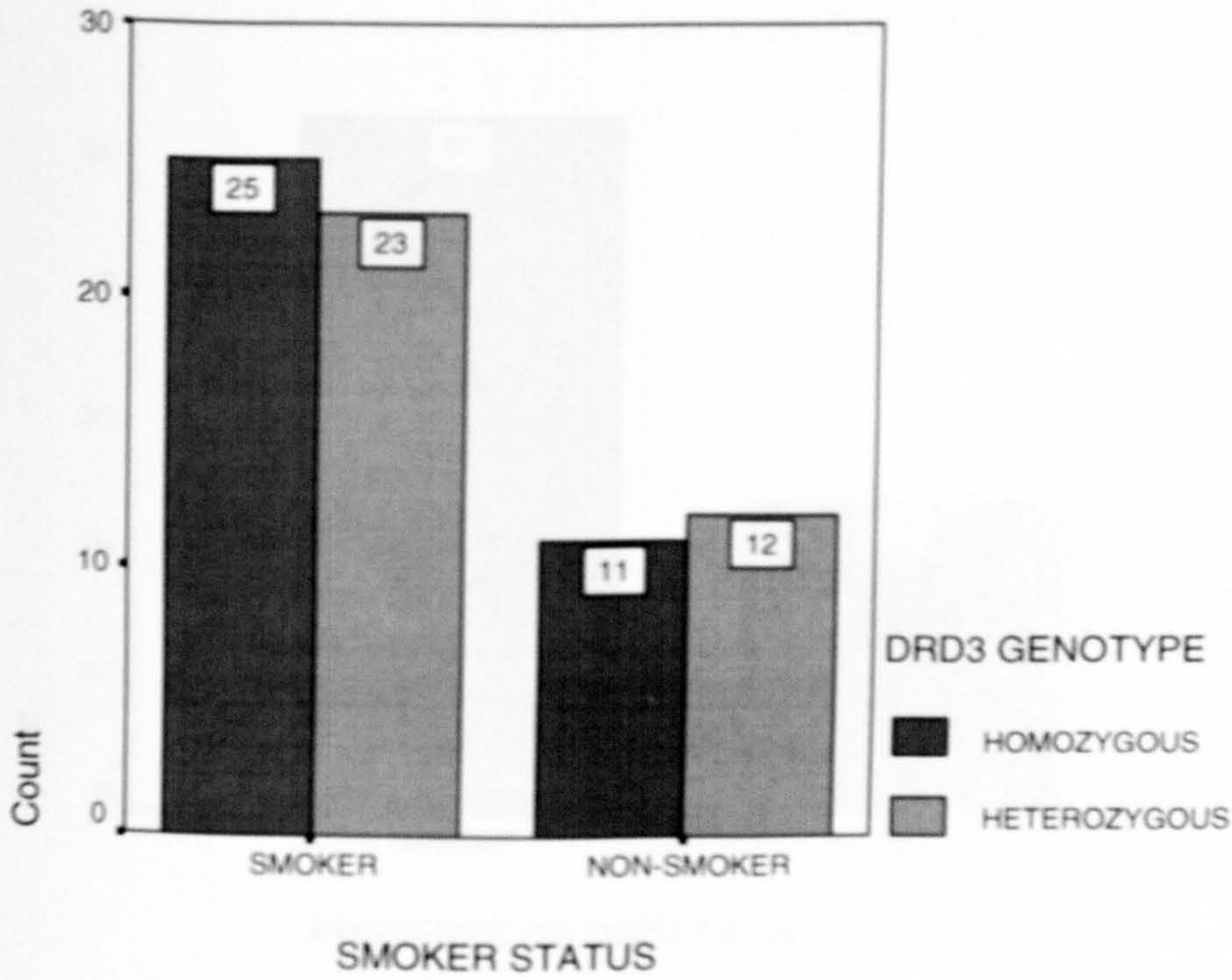


Figure 4.6 **Graph showing incidence of DRD4 genotypes in entire sample.**

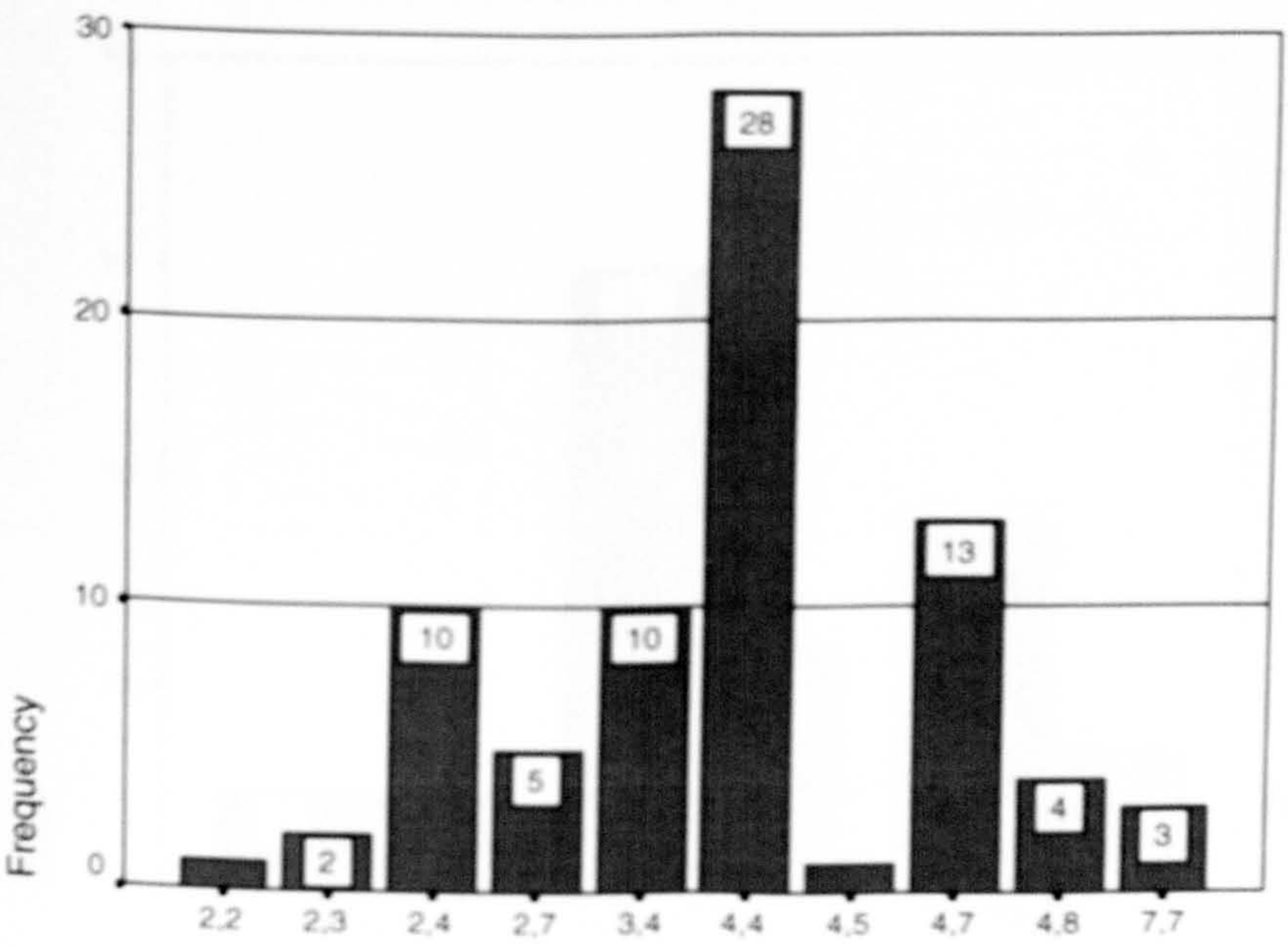


Figure 4.7 **Graph showing incidence of DRD4 L allele (D4.7 and D4.8) in entire sample.**

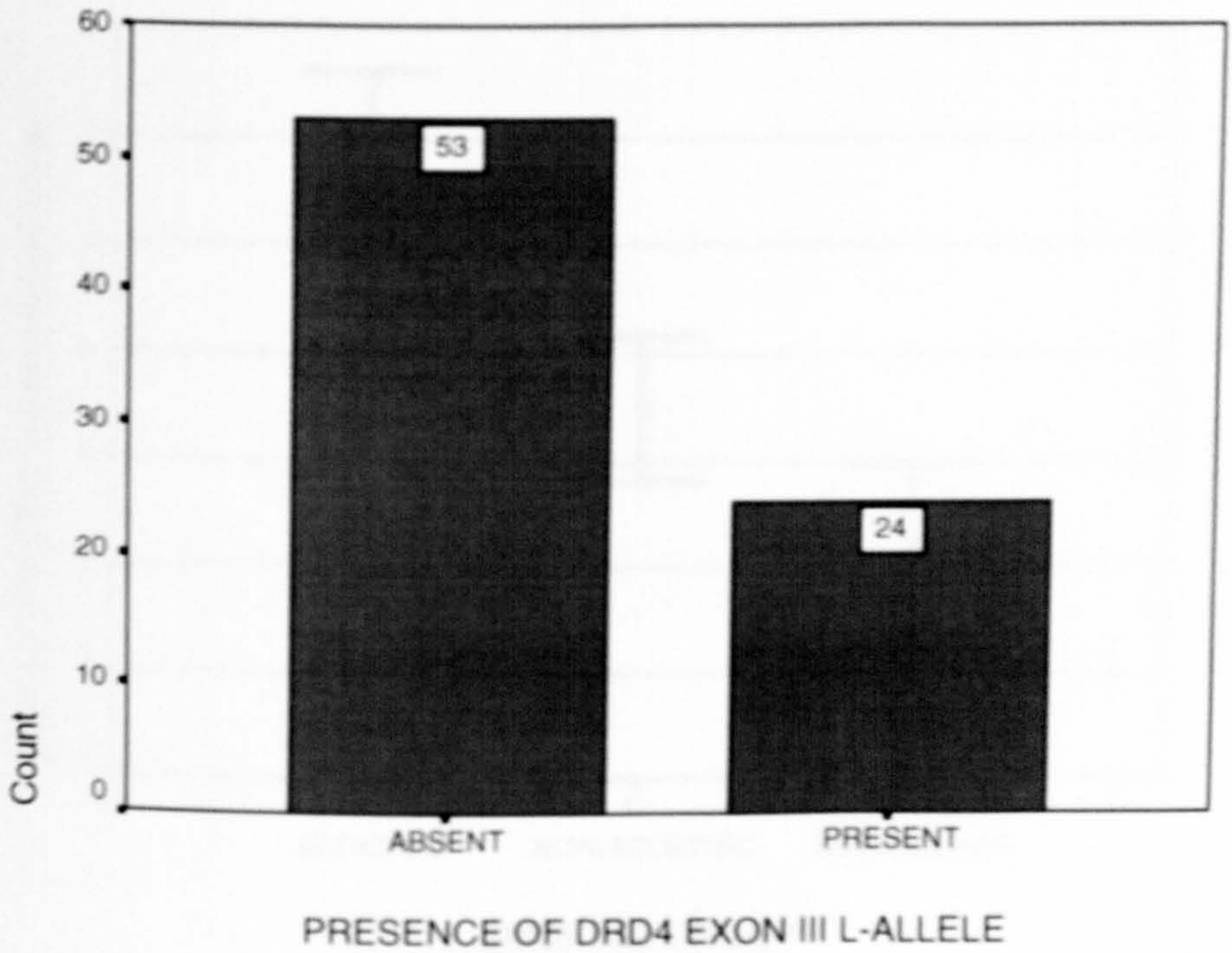


Figure 4.8 **Graph showing distribution of DRD4 L-allele incidence according to addicted smoker, non-addicted smoker or non-smoker status.**

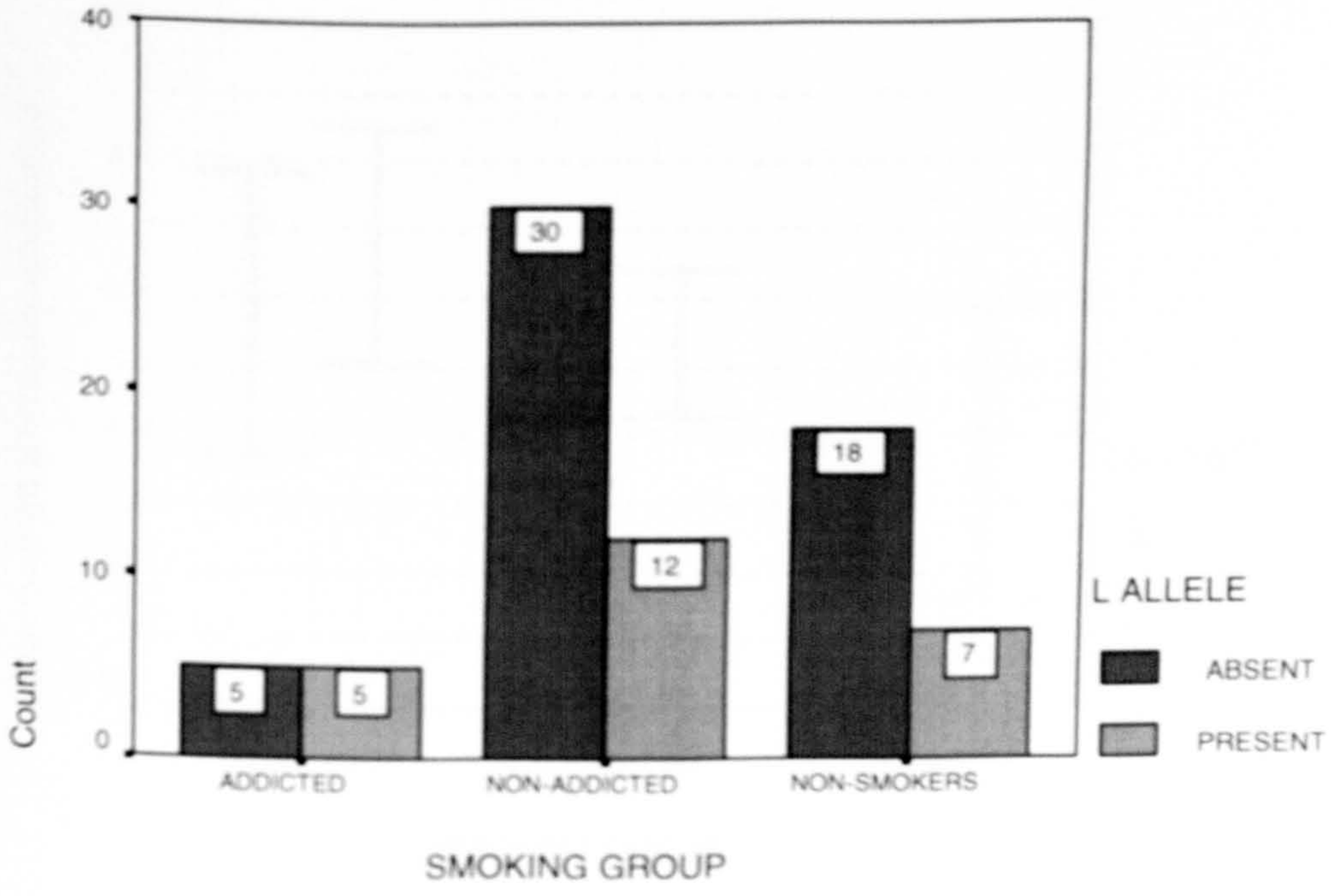


Figure 4.9 **Graph showing mean Impulsiveness subscale scores according to addicted smoker, non-addicted smoker or non-smoker status.**

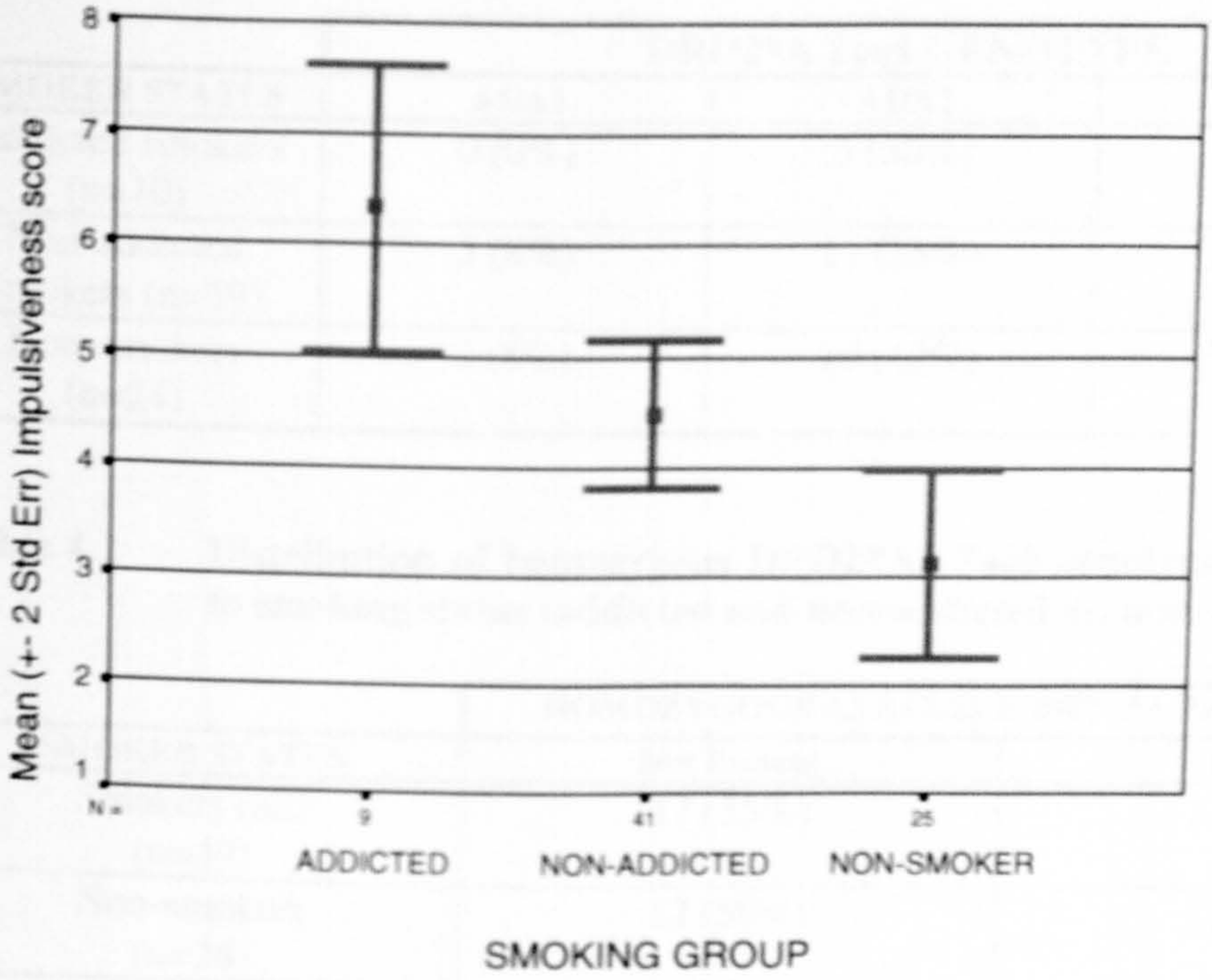


Figure 4.10 **Graph showing mean Impulsiveness score according to smoking group and presence or absence of DRD4 L-allele.**

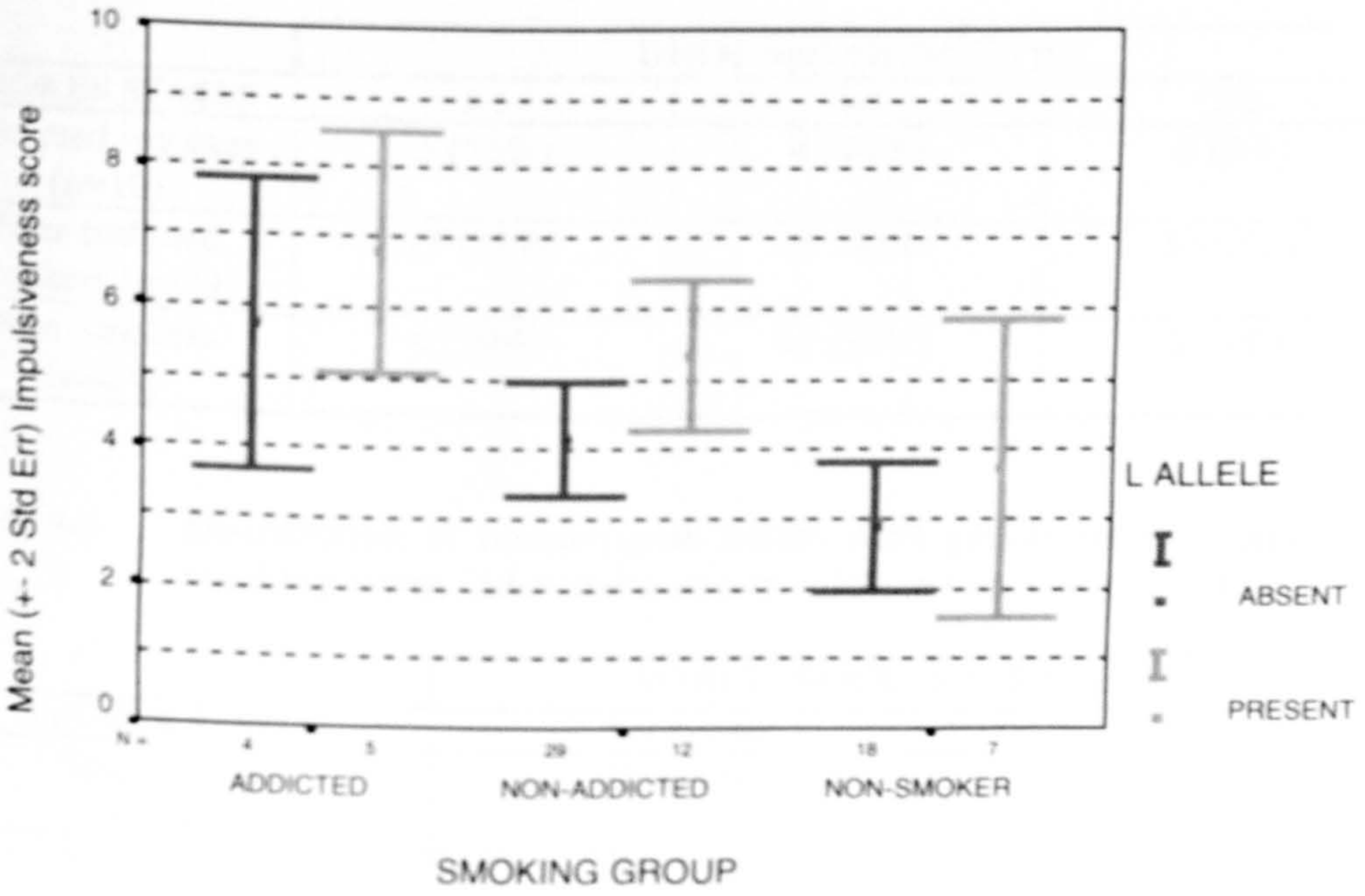


Table 4.1 Distribution of DRD2*A *TaqI* genotypes in relation to smoking status.

	DRD2*A *TaqI* GENOTYPE		
SMOKER STATUS	A1/A1	A1/A2	A2/A2
Addicted smokers (n=10)	0 (0%)	3 (30%)	7 (70%)
Non-addicted smokers (n=39)	3 (8%)	11 (28%)	25 (64%)
Non-smokers (n=24)	2 (8%)	10 (42%)	12 (50%)

Table 4.2 Distribution of homozygous DRD2*A2 *TaqI* genotypes in relation to smoking status (addicted and non-addicted vs. non-smokers).

	HOMOZYGOUS A2 ALLELE DRD2*A *TaqI* GENOTYPE	
SMOKER STATUS	Not Present	Present
Smokers (all) (n=49)	17 (35%)	32 (65%)
Non-smokers (n=24)	12 (50%)	12 (50%)

Table 4.3 Distribution of DRD3 *BalI* genotypes in relation to smoking status.

	DRD3 *BalI* GENOTYPE		
SMOKER STATUS	1-1	1-2	2-2
Addicted smokers (n=10)	5 (56%)	4 (44%)	0 (0%)
Non-addicted smokers (n=39)	15 (38%)	19 (49%)	5 (13%)
Non-smokers (n=24)	9 (39%)	12 (52%)	2 (9%)

Table 4.4 Distribution of homozygous DRD3 *BalI* genotypes in relation to smoking status (addicted and non-addicted vs. non-smokers).

	HOMOZYGOUS DRD3 *BalI* GENOTYPE	
SMOKER STATUS	Not Present	Present
Smokers (all) (n=48)	23 (48%)	25 (52%)
Non-smokers (n=23)	12 (52%)	11 (48%)

Table 4.5 Total incidence of DRD4 exon III allelic polymorphisms

	D4.2	D4.3	D4.4	D4.5	D4.7	D4.8
No. of subjects presenting (%)	18 (23%)	11 (14%)	66 (86%)	1 (1.3%)	21 (27%)	4 (5%)

Table 4.6 Mean Novelty Seeking (and subscale) scores in relation to presence of DRD4 exon III L-allele (D4.7 or D4.8)

L-allele status	Novelty Seeking	Sub-scale 1 (Exploratory)	Sub-scale 2 (Impulsiveness)	Sub-scale 3 (Extravagance)	Sub-scale 4 (Disorderliness)
ABSENT (n=51)	22.6 ± 5.9	7.3 ± 2.1	3.8 ± 2.2	6.0 ± 2.5	5.4 ± 1.9
PRESENT (n=24)	25.6 ± 6.3*	7.7 ± 1.9	5.2 ± 2.4**	6.5 ± 2.2	6.3 ± 2.1

Absent versus present: * significance p<.05 ** significance p<.025

Table 4.7 Mean Novelty Seeking (and subscale) scores for non-smokers, addicted and non-addicted smokers

Smoking Group	Novelty Seeking	Sub-scale 1 (Exploratory)	Sub-scale 2 (Impulsiveness)	Sub-scale 3 (Extravagance)	Sub-scale 4 (Disorderliness)
ADDICTED SMOKERS (n=9)	28.6 ± 5.2^{c}	7.8 ± 1.6	6.3 ± 1.9^{c}	7.6 ± 1.4^{b}	6.9 ± 1.5^{b}
NON-ADDICTED SMOKERS (n=40)	24.3 ± 6.1^{b}	7.3 ± 2.2	4.6 ± 2.2^{b}	6.5 ± 2.3^{a}	6.0 ± 2.1^{a}
NON-SMOKERS (n=25)	$20.4 \pm 5.1^{b,c}$	7.4 ± 1.9	$3.1 \pm 2.2^{b,c}$	$5.1 \pm 2.5^{a,b}$	$4.8 \pm 1.9^{a,b}$

Differences between Smoking Groups: [a] – significance p<.05, [b] – significance p<.025, [c] – significance p<.001

Chapter 5 – Psychosocial differences between addicted and non-addicted smokers

5.1 Introduction

In Britain, approximately 28% of men and 26% of women are regular smokers (Omnibus Survey, 1997). Many smokers commence the behaviour aged 12-15, with adult prevalence peaking in the 20-24 age bracket (Department of Health Bulletin, 1998). There is a paucity of contemporary research investigating personality and psychosocial variables that might discriminate or predict smoking behaviour. The initiation of smoking has been attributed to environmental factors such as peer group pressure and adult modelling (Eysenck, 1980; Presti et al. 1992; Rowe et al. 1992), although theories of smoking persistence have focused on the relationship between smoking behaviour and psychoactive effects. This conceptualises personality interacting with internal and external environmental factors to produce motivational conditions conducive to smoking (Eysenck, 1980).

Previous research reports that 90% of smokers meet DSM-III criteria for tobacco dependence (Hughes, Gust & Pechacek, 1987), and that 90% of adolescents who smoke as few as 3 or 4 cigarettes progress to complete dependence (Russell, 1990). For these reasons, nicotine has come to be regarded as an addictive substance. Smoking behaviour has been explained in terms other than dependence; people may smoke in order to obtain positive reinforcing effects of nicotine, possibly including enhancement of cognitive performance (Wesnes & Warburton, 1983b). The latter theory is contentious since a *tobacco withdrawal syndrome* has been demonstrated, which impairs cognitive performance (Snyder, Davis & Henningfield, 1989).

It has also been theorised that smoking and other drug use is associated with levels of ability to cope effectively with stress. The *stress-coping* model of addiction proposes that in the absence of more effective or appropriate coping strategies, individuals use drugs as a means of coping with stress (Alexander & Hadaway, 1982; Wills & Shiffman, 1985). These theories purport a role for perceived stress, coping abilities and strategies, and social support in drug use, although it has been argued that the persistent cycle of withdrawal in habitual smoking itself causes stress (Parrott, 2000). If this is the case, smoking is conceivably the solution to a problem of its own creation. Parrott & Kaye (1999) reported that abstinent smokers experienced greater daily stress and cognitive failures (absent-mindedness) than non-abstinent smokers, which may be a direct result of the tobacco withdrawal syndrome or due to the removal of a stress-reducing or attention-enhancing agent (i.e. nicotine).

Smokers could conceivably be using tobacco as a pharmacological coping strategy in the absence of other stress buffers (e.g. social support) that may be less risky or physically damaging than smoking. The presence of interactions between stress and social support in smokers is not well researched; although studies have shown that successful quitting is associated with higher levels of support (e.g. West, McEwen, Bolling & Owen, 2001; Carlson, Goodey, Hahn Bennett, Taenzer & Koopmans, 2002). Specific support, such as from a spouse/partner, has not been shown to be associated with smoker/non-smoker status (Rehm, Fichter & Elton, 1993).

Dependent smoking is associated with major depression and anxiety disorders (Covey, Glassman & Stetner, 1998; Bergen & Caporaso, 1999; Degenhart, Hall & Lynskey, 2001). These associations or comorbidity is interesting, and research into

the relationship between smoking behaviour and affective psychiatric disorders is growing. For example, smokers may be using tobacco to self-medicate their mood problems. Alternatively, it might be that the perpetual diurnal cycle of withdrawal and reinstatement leads to increased anxiety and dysphoria (West & Hajek, 1997).

There is evidence that habitual smoking could cause reductions in 5-HT release in the hippocampus (Benwell, Balfour & Anderson, 1990). As studies have shown that increased stimulation of 5-HT_{1A} receptors in the hippocampus may be implicated in anxiety (Andrews et al. 1994), it is possible smokers are benefiting from nicotine-induced reductions in hippocampal 5-HT, thus pharmacologically reducing baseline levels of anxiety. This is concordant with human studies suggesting that 'nicotine reduces anxiety and negative affect in chronic smokers' (Gilbert & Wesler, 1989).

A number of prospective studies support the theory that smokers may be using nicotine to reduce anxiety. Several of these have reported associations between anxious, aggressive, depression-prone and generally neurotic personality traits in childhood and the tendency to take up smoking later in life (Brown et al. 1996; Cherry & Kiernan, 1978; Kandel & Davies, 1986; Seltzer & Oechsli, 1985). Alternatively, dysphoric individuals being less able to quit may explain this association. Anda et al. (1990) reported that depressed smokers were 40% less likely to quit compared with non-depressed smokers. Furthermore, Covey et al. (1990) reported that smokers with a history of depression experienced more severe withdrawal symptoms (especially depressed mood and difficulty concentrating) than the group without such a history. Persistent depressive symptoms are shown to be prospective predictors of increased cigarette use across time, after controlling for baseline levels of smoking (Windle &

Windle, 2001). Proponents of this 'self-medication' hypothesis suggest that many of the negative affective symptoms associated with the tobacco withdrawal syndrome represent the unmasking of psychopathology that had been controlled by smoking (Goldstein, 1987; Hughes & Hatsukami, 1987).

Smoking has been reported to be associated with a variety of negative health-related behaviours. There is a well-documented positive association between alcohol consumption and smoking (e.g. Shiffman & Balabanis, 1995), as well as associations between smoking and both physical inactivity (Wankel & Sefton, 1994) and unhealthy diet (Dallongueville, Marécaux & Fruchart, 1998). These associations are a major concern since evidence suggests that the risk of mortality elevates with increasing numbers of unhealthy behaviours (Wingard, Berkman & Brand, 1982). Furthermore, smokers are shown to have more limited expectations of health, perceived lower effectiveness of health-promoting behaviours and more situational motivations to engage in negative health behaviours (Chamberlain & O'Neill, 1998).

"Chippers", or non-dependent regular smokers (Shiffman, 1989) have also received little psychosocial profiling. Kassel, Shiffman, Gnys, Paty & Zettler-Segal (1994) found no differences between chippers and dependent smokers in terms of perceived stress, coping or social support. However, as the authors themselves pointed out, their dependent smokers group may have been unrepresentative since they were closely matched to the chippers group and featured an unusually high proportion of females, and a low average cigarette nicotine yield. Kassel et al. (1994) reported dependent smokers having modest personality differences to chippers, with higher impulsivity and lower self-control.

The current study aims to identify whether there are particular psychosocial markers that could potentially discriminate addicted from non-addicted smokers. Since psychosocial measures can be subtle and highly sensitive, a battery of several instruments was used to maximise the scope of the study. Although it is difficult to attribute causality (in terms of both existence and direction) between smoker status and many of these variables, understanding that the associations exist may provide useful indications of groups particularly at risk of developing tobacco dependence.

The following hypotheses were tested:

I. that psychosocial profiles of smokers and non-smokers would differ significantly; particularly that smokers would have greater perceived stress, psychological disturbance, prevalence of cognitive failures, and have lower social support, health values and expectancies.

II. that psychosocial profiles of addicted and non-addicted smokers would differ significantly; particularly that addicted smokers would have greater psychological disturbance, and perceived stress, and have lower social support.

5.2 Method

5.2.1 Design

This between subjects design examined the psychosocial profiles of addicted smoker (n=10), non-addicted smoker (n=39) and non-smoker (n=25) groups. Details regarding the grouping of subjects are described in Chapter 2. Instruments measured subjects' health-related behaviours, social support, loneliness, self-esteem, internal

and external control, life events, perceived stress, health values and expectancies, cognitive failures, psychological and somatic well-being and physical symptoms.

5.2.2 Subjects

Subjects (N=74) age ranged from 18 to 54 (mean 24.5), 35 males, 39 females. Fifty-two subjects (70%) participated as part of the mood and cognitive performance study presented in Chapter 3. Twenty-two subjects (30%) were recruited only for the questionnaire study detailed in Chapter 2. Twelve questionnaire booklets were incomplete, however all completed individual instruments were included in analyses. A full description of the subject sample and recruitment information is included in Chapters 2 and 3.

5.2.3 Measures

Demographics

These data (sex, age, etc.) were cross-referenced from the Smoking Questionnaire Battery discussed in Chapter 2.

Psychosocial Questionnaire Measures

The following instruments were administered as a large questionnaire booklet. Copies of these questionnaires may be seen in Appendix XIII.

a) Health Related Behaviours: Cohen et al (1991)

This questionnaire contained 27 items covering eating, sleeping, drinking, smoking and exercise behaviours. Response scales often differed according to each item.

b) Interpersonal Support Evaluation List (ISEL)

Social support was measured by the ISEL (Cohen and Hoberman, 1983), a 40-item questionnaire relating to perceived level of current support; each item was scored on a 4-point scale. Four subscales were derived: Tangible support (the availability of material help), Appraised support (someone available to talk to), Belonging (availability of someone to do things with), and Self-esteem support (positive comparison of oneself to others). These subscales were also totalled to yield an overall ISEL score, covering all areas of social support in general life. Cohen et al. (1985) calculated an internal reliability (Alpha coefficient) of .88 to .90.

c) Social Network Index (SNI): Berkman (1984)

This 12-item questionnaire was split into 3 sections. Section 1a) and Section 3 were answered by circling yes/no, while the other questions were responded to on a 5-point Likert-type scale. This yielded a total SNI score indicating size and frequency of respondents social network.

d) University of California Loneliness Scale (UCLA): Russell, Peplau and Ferguson (1978)

This 20-item questionnaire measured frequency of feelings of loneliness. Subjects responded on a 5-point Likert-scale (0=never, 1=almost never, 2=sometimes, 3=fairly often, 4=very often). These items yielded a total loneliness score.

e) Self-esteem scale (SE): Fleming and Watts (1981)

This was a 14-item questionnaire on which subjects responded using a 6-point Likert-type scale (1= "I agree very much", to 6= "I disagree very much"). This yielded a total Self-Esteem score.

f) Social Reaction Inventory (SRI)

Control over non-job life was measured by two scales from The Social Reaction Inventory (Paulhus, 1983), consisting of 10 items per scale, scored on a 6-point response scale. The questionnaire asked respondents to state how they 'usually feel', implying an ongoing state. Responses were scored in these two main areas, Control over interpersonal relationships, and Control over personal life. The two scales were also summated to yield an overall score. Alpha coefficients for reliability are reported as .75 and .77 respectively, and the convergent validity for both scales fell between .30 and .37. Paulhus (1983) reported that the correlates of each scale were largely independent, and showed good discriminant validity.

g) Life Events List

This was a modified version of the Life Events Scale (Cohen, Tyrell & Smith, 1993), which measured both positive and negative life events, and also provided a total score, which was a composite of the two subscales. It consisted of a 24-item scale ascertaining whether specific life events have occurred during the past 12 months.

h) Perceived Stress Scale (PSS)

This 14-item questionnaire was developed by Cohen et al (1983), and measured the degree to which subjects find their lives overloading, unpredictable and

uncontrollable. Participants were also asked questions about their current levels of experienced stress. Responses were made using a 5-point Likert-type scale (0 = never, 1=almost never, 2=sometimes, 3=fairly often and 4=very often).

i) Health Promotion Scale

This questionnaire was devised by Bausell (1986), and consists of 19 health-related questions. These cover eating habits, health checkups i.e. visits to the doctor and dentist to exercising, alcohol consumption, smoking and sleep patterns. Subjects respond by circling 'yes' or 'no' to each question.

j) Health Orientation Scale

This 50-item questionnaire (Snell, Johnson, Lloyd & Hoover, 1991) measures several subscales of psychological tendencies associated with health. These include Health consciousness, Health anxiety, Health confidence, Motivation not to be unhealthy, Motivation to be healthy, Health Internal Locus of Control, Health External Locus of Control and Health Status. Subjects respond to each question on a 5-point Likert scale (1=not at all characteristic of me, 2=slightly characteristic of me, 3=somewhat characteristic of me, 4=moderately characteristic of me and 5=very characteristic of me).

k) Cognitive Failures Questionnaire

Devised by Broadbent, Cooper, Fitzgerald and Parkes (1982), this 25-item questionnaire measures lapses of memory whilst undertaking tasks (e.g. forgetting appointments). Subjects respond to each question on a 5-point Likert scale (0=never,

1=very rarely, 2=occasionally, 3=quite often and 4=very often) by circling how often each cognitive failure occurs.

l) Middlesex Hospital Questionnaire

This adapted version of the original MHQ (Crown-Crisp Experiential Index; Crown & Crisp, 1979) was based on that used by Broadbent et al. (1984). The questionnaire featured 28 items, and responses were registered using a 3-point scale (typically 0=never, 1=sometimes, 2=often). Respondents were asked to consider each item in the context of "during the last six weeks". The MHQ generated four scores for various kinds of symptoms: Anxiety, Obsessional Symptoms, Somatic Symptoms and Depression, as well as a somewhat different short scale of Obsessional Personality.

m) Cohen and Hoberman Inventory of Physical Symptoms (CHIPS)

This scale was devised by Cohen and Hoberman (1983), and consisted of 12 statements related to physical symptoms. Subjects were required to indicate how much each physical symptom had bothered or distressed them during the last month. Responses were made using 5-point Likert-type scales (0=not at all, 1=a little bit, 2 = moderately, 3 = quite a bit and 4 = extremely). A total score was obtained by summing frequency responses across the range (i.e. 1 to 48). Previous studies conducted by Cohen and Hoberman (1983), using student populations have found the internal reliability to be 0.88 (Cronbachs alpha).

n) Symptom Checklist

This questionnaire was in two parts. Part 1 presented respondents with 27 common physical symptoms with checkboxes next to them. Participants were asked to tick the

boxes of any symptoms they were currently experiencing. Part 2 asked subjects to indicate which, if any, prescribed drugs or multivitamins, etc. they were currently taking.

5.2.4 Procedure

Subjects were given Psychosocial Questionnaire Booklets at first face-to-face contact with researchers, and asked to answer the questions in their own time. Subjects reported taking approximately 40 minutes to complete the booklet.

5.2.5 Statistical analyses

The main effect of group on the numerous subscales and factors of the various instruments examined were analysed using univariate analysis of variance (ANOVA). Specific differences between the three groups were examined using the Tukey post-hoc test. Statistics were performed using the Statistical Package for Social Sciences version 9.0. Correction for multiple comparisons was considered unnecessary since each component was analysed in its own right, and many of the instruments would yield highly correlated results.

5.3 Results

The psychosocial differences between smokers and non-smokers are examined in Section 5.3.1, while Section 5.3.2 presents differences between the two smoking groups. The relationship between levels of tobacco dependence and levels of psychological disturbance is presented in Section 5.3.3.

5.3.1 Psychosocial differences between smokers and non-smokers

Results are reported where there were significant main effects of group, and Tukey post-hoc analyses demonstrated significant differences between non-smokers and *both groups* of smokers. Mean scores for each group on the different psychosocial variables are reported in Table 5.1.

No significant differences were observed between smokers and non-smokers in variables pertaining to health-related behaviours, perceived levels of social support, individuals' loneliness, levels of self-esteem, measures of internal and external control, life events, psychological and somatic well-being or total number of current physical symptoms.

5.3.1.1 Perceived Stress

Scores on the Perceived Stress Scale were affected by group ($F\{2,70\}=3.30$, $p<.05$). Tukey post-hoc analysis showed non-significant trends for non-smokers to have lower perceived stress than both addicted and non-addicted smokers (both $p<.10$) (Figure 5.1).

5.3.1.2 Health values and expectancies

Several variables on the Health Orientation Scale demonstrated group effects. 'Health Confidence' factor scores were significantly affected by group ($F\{2,70\}=6.80$, $p<.01$). Tukey post-hoc analysis demonstrated that non-smokers had significantly higher 'Health Confidence' scores than both addicted smokers ($p<.05$) and non-addicted smokers ($p<.01$) (see Figure 5.2).

'Motivation to not be unhealthy' factor scores were different between the groups ($F\{2,71\}=12.73$, $p<.001$). Tukey post-hoc analysis demonstrated that non-smokers had significantly higher 'Motivation to not be unhealthy' factor scores than both addicted and non-addicted smokers (both $p<.001$) (Figure 5.3).

'Motivation to be healthy' factor scores were also different between the groups ($F\{2,71\}=9.93$, $p<.001$). Tukey post-hoc analysis demonstrated that non-smokers had significantly higher 'Motivation to be healthy' factor scores than both addicted smokers ($p<.01$) and non-addicted smokers ($p<.001$) (Figure 5.4).

5.3.1.3 Cognitive failures

The prevalence of cognitive failures (total CFQ score) was significantly affected by group ($F\{2,69\}=4.93$, $p<.01$). Tukey post-hoc analysis showed that non-smokers had fewer cognitive failures than addicted smokers ($p<.025$) and non-addicted smokers ($p<.05$) (Figure 5.5).

5.3.2 Psychosocial differences between addicted and non-addicted smokers

Results are reported where there were significant main effects of group, and Tukey post-hoc analyses demonstrated significant differences between non-addicted smokers and addicted smokers. Mean scores for each group on the different psychosocial variables are reported in Table 5.1.

No significant differences were observed between addicted smokers and non-addicted smokers in variables pertaining to health-related behaviours, perceived levels of social support, individuals' loneliness, levels of self-esteem, measures of internal and

external control, life events, perceived stress, health values and expectancies or total number of current physical symptoms.

5.3.2.1 Psychological and somatic well-being

Two factors on the Middlesex Hospital Questionnaire demonstrated group effects. Anxiety factor scores were significantly affected by group ($F\{2,67\}=4.05$, $p<.025$). Tukey post-hoc analysis demonstrated that addicted smokers had significantly higher Anxiety scores than non-addicted smokers and non-smokers (both $p<.05$) (see Figure 5.6).

Depression factor scores were also different between the groups ($F\{2,69\}=4.63$, $p<.025$). Tukey post-hoc analysis demonstrated that addicted smokers had significantly higher Depression scores than both non-addicted smokers and non-smokers (both $p<.05$) (Figure 5.7).

5.3.3 Levels of tobacco dependence and psychosocial correlates

Adjunctive to the result that Depression and Anxiety subscales of the MHQ differ between addicted and non-addicted smoker groups, the associative relationship between these subscale factor scores and level of tobacco dependence was investigated. Spearman's Rho correlation was used to examine the association between Anxiety and Depression factor scores and Addiction Index scores.

Frequency analysis identified a single Depression factor score outlier that was removed prior to correlation analysis. Depression factor scores were positively correlated with Addiction Index scores ($r=3.89$, $p<.01$; 2-tailed) (Figure 5.8). Anxiety

factor scores were not correlated with Addiction Index scores (r=0.157, p=0.29; 2-tailed).

5.4 Discussion

The major findings of this study were that smokers have greater perceived stress and cognitive failures than non-smokers. Smokers had significantly lower motivation toward healthy behaviours and to avoid unhealthy behaviours, and had lower confidence in their health than non-smokers. Addicted smokers reported more psychological disturbance, particularly greater anxiety and depression than non-addicted smokers. Furthermore, levels of tobacco dependence were positively correlated with depression.

As predicted, there were significant psychosocial differences between smokers and non-smokers. The observed trend for non-smokers to report lower perceived stress than both smoking groups is not consistent with the findings of Kassel et al. (1994), who reported no differences in levels of perceived stress between non-smokers, regular smokers and chippers. The current results suggest that smokers have greater perceived stress than non-smokers, although the existence or direction of causality cannot be inferred. Smokers may be self-medicating in order to reduce perceived stress levels (Wills & Shiffman, 1985).

The current findings are concordant with the theories and findings of Parrott (2000; 1995a; 1995b; Parrott & Kaye, 1999), who has consistently found higher baseline stress levels in smokers than non-smokers. Parrott (2000) explains these results not in terms of a pre-morbid condition or greater objective stress, but as an effect of

smoking; i.e. a stress-inducing persistent cycle of withdrawal and reinstatement. Current findings do not entirely support this theory, since it would predict there to be differences in perceived stress between addicted and non-addicted smokers, a finding not observed. In order to clarify this issue, prospective research should look at perceived stress levels before and after initiation of smoking behaviour.

Smokers, particularly the addicted group, reported having more prevalent cognitive failures than non-smokers. Although no directly comparable previous research has been carried out, Parrott & Kaye (1999) found that abstinent smokers had more cognitive failures than non-abstinent smokers over the course of a normal day, although non-abstinent smokers did not differ from non-smokers. Parrott & Kaye (1999) interpret their findings as support for the deprivation reversal model of tobacco use. Following from this, cognitive failures (or absent-mindedness) may be an indirect measure of withdrawal. In the case of the current findings, the differences between smokers and non-smokers may reflect episodes of acute tobacco withdrawal throughout the day, leading to attentional deficits (Snyder, Davis & Henningfield, 1989) that manifest as perceived cognitive failures or absent-mindedness. These may even act as internal/cognitive cues to initiate smoking behaviour. Alternatively the cognitive failures may not be related to acute episodes of withdrawal. Smokers might be self-medicating in an attempt to improve poor baseline cognitive performance.

Smokers and non-smokers were shown to have different health value and health orientation profiles. Smokers were more anxious and less confident about their health than non-smokers. This is broadly consistent with Chamberlain & O'Neill's (1998) findings that smokers had lower expectations of health and lower perceived

effectiveness of health-promoting behaviours. Furthermore, they were less motivated to be healthy and less motivated not to be unhealthy. This is consistent with Chamberlain & O'Neill's (1998) results showing that smokers report greater situational pressures to engage in negative health behaviours. These findings demonstrate to some degree that smokers were aware that their smoking compromises their health. Furthermore, they may be reacting to the cognitive dissonance created by their smoking behaviour by devaluing both health-promoting behaviour and their own health *per se*.

No differences were shown between smokers and non-smokers in terms of perceived social support. These findings are consistent with Kassel et al. (1994), who showed no differences between smokers and non-smokers in the amount of social support experienced. This has implications for the stress-coping model of smoking (Wills & Shiffman, 1985), as it suggests that levels of non-drug stress buffering are comparable between non-smokers and smokers. It seems less likely therefore that smokers are making up for shortfalls in alternative sources of coping or support by using tobacco. Perceived social support is viewed as a more sensitive indicator of its stress-buffering effects than objective existence of the resource (Blazer, 1982). This is because the appraisal of stress is based on a person's beliefs about available support as opposed to its actual availability (Cohen et al. 1985).

Psychological disturbance such as symptoms of anxiety, depression, somatic complaints and obsessive behaviour were not shown to differ significantly between smokers and non-smokers. This finding was unexpected, since previous research suggests smokers tend to be more anxious (West & Hajek, 1997; Parrott, 1999) and

more depressed (Degenhart et al. 2001) than non-smokers. As discussed later however, group differences were teased out, as addicted smokers had greater anxiety and depressive symptoms than both non-addicted smokers and non-smokers. The cited previous research above utilised large samples where presence of nicotine dependence was estimated at 55-87% (Woody, Cottler & Cacciola, 1993), whereas only 33% of the current sample was designated as dependent. Differences in categorization, contrasts used and relative proportions of dependent tobacco users are therefore presented as explanations for these findings.

There were few psychosocial variables that statistically significantly differed between addicted and non-addicted smokers, however those that did were highly salient and interesting. No differences were observed between addicted and non-addicted smokers in terms of perceived stress. This finding is consistent with those of Kassel et al. (1994) as presented earlier, but is not consistent with Shiffman (1989). Shiffman (1989) found that dependent smokers had higher levels of subjective stress as measured by the Perceived Stress Scale than chippers. Of course, current results are not directly comparable with Shiffman's studies as chippers are likely to be a subset rather than a synonym of non-addicted smokers. The non-addicted smokers group in the current study may have contained some moderately dependent smokers or even dependent smokers who were under-reporting their addictive status in previous smoking-related questionnaires.

Furthermore, there were no differences between addicted and non-addicted smokers levels of perceived social support. As above, this is consistent with the findings of Kassel et al. (1994), who reported that the amount of social support experienced did

not discriminate chippers from regular smokers. Shiffman (1989) however, found that chippers had significantly higher total perceived support demonstrated by higher total ISEL scores than dependent smokers.

The current findings suggest that stress and coping variables are not relevant to non-addicted smokers absence of (or protection from) tobacco dependence. It does not support the theory that dependent smokers feel the "need" to smoke more than their non-dependent counterparts as they perceive greater stress and have less appropriate coping strategies. Again, it might be argued that the heterogeneity of the non-addicted smokers group and the small number of addicted smokers may be masking important differences in these variables.

Addicted and non-addicted smokers differed significantly on two factors of psychological disturbance measured by the MHQ. Addicted smokers had higher Anxiety and Depression symptoms than non-addicted smokers. This is consistent with previous research showing that tobacco dependence is associated with anxiety and affective disorders (e.g. Covey et al. 1998).

These current findings are particularly interesting since they show non-smoker and non-addicted smoker groups with almost identical means and variance, but with the addicted smokers demonstrating considerably higher scores. Unfortunately, the existence and direction of a causal relationship between anxious and depressive symptoms and tobacco dependence cannot be elucidated by these results. It is possible that smokers are becoming tobacco dependent through self-medicating their pre-morbid mood disorder(s). Alternatively, the cycle of withdrawal and reinstatement

that characterises nicotine dependence may be either directly or indirectly generating more depressive or anxious episodes. Evidence for both phenomena exist (Windle & Windle, 2001; Brown et al. 1996; Parrott, 2000), and it is possible that both mechanisms could be acting in tandem, which would offer further explanation why nicotine is a drug that is considered disproportionately difficult to give up.

There was a positive correlation between level of tobacco dependence and prevalence of depressive symptoms on the MHQ, strengthening the validity of the association discussed in the previous paragraph. This observed relationship between dysphoria and nicotine addiction is clearly important. Windle & Windle (2001) found that serious and persistent depressive symptoms were prospective predictors of increased cigarette use across time, after controlling for baseline measures. More prospective studies should attempt to replicate these findings, so it can be identified if adolescents with even mild affective disorders are at increased risk of tobacco dependence.

Greater numbers of subjects in the addicted smokers group would have been desirable, as this would possibly have made some of the trends significant and elucidated further psychosocial differences between the three groups. One important factor missing from the psychosocial profile generated in this research was socio-economic status. This has been shown to be associated with smoking (Chamberlain & O'Neill, 1998), levels of social support (Turner & Marino, 1994) and psychological distress and depression (Ulbrich, Warheit & Zimmerman, 1989). It would have been useful to add socio-economic status as a covariate when performing the analyses to ensure that relationships between the three groups were independent of other commonly associated factors.

The findings presented in this chapter suggest that smokers generally experienced greater perceived stress and reported more cognitive failures than non-smokers, possibly reflecting either baseline psychological differences or feedback from the cycle of withdrawal and reinstatement associated with the tobacco withdrawal syndrome. Smokers also have different health orientations to non-smokers, characterised by greater anxiety about health, lower health confidence and motivations to be healthy. Addicted smokers were shown to have more anxious and depressive symptoms than non-addicted smokers. Prospective studies should be undertaken to clarify the relationship between affective disorders and tobacco dependence, as this may elucidate the existence or direction of causality in the association. This could allow groups at particular risk of depression and anxiety, or addiction to smoking, to be targeted and informed or treated.

Figure 5.1 **Error-bar graph showing mean scores on the Perceived Stress Scale for non-smokers, addicted and non-addicted smokers.** Error bars represent ±2 standard errors of the group mean scores (n=74; addicted smokers n=10, non-addicted smokers n=39, non-smokers n=25).

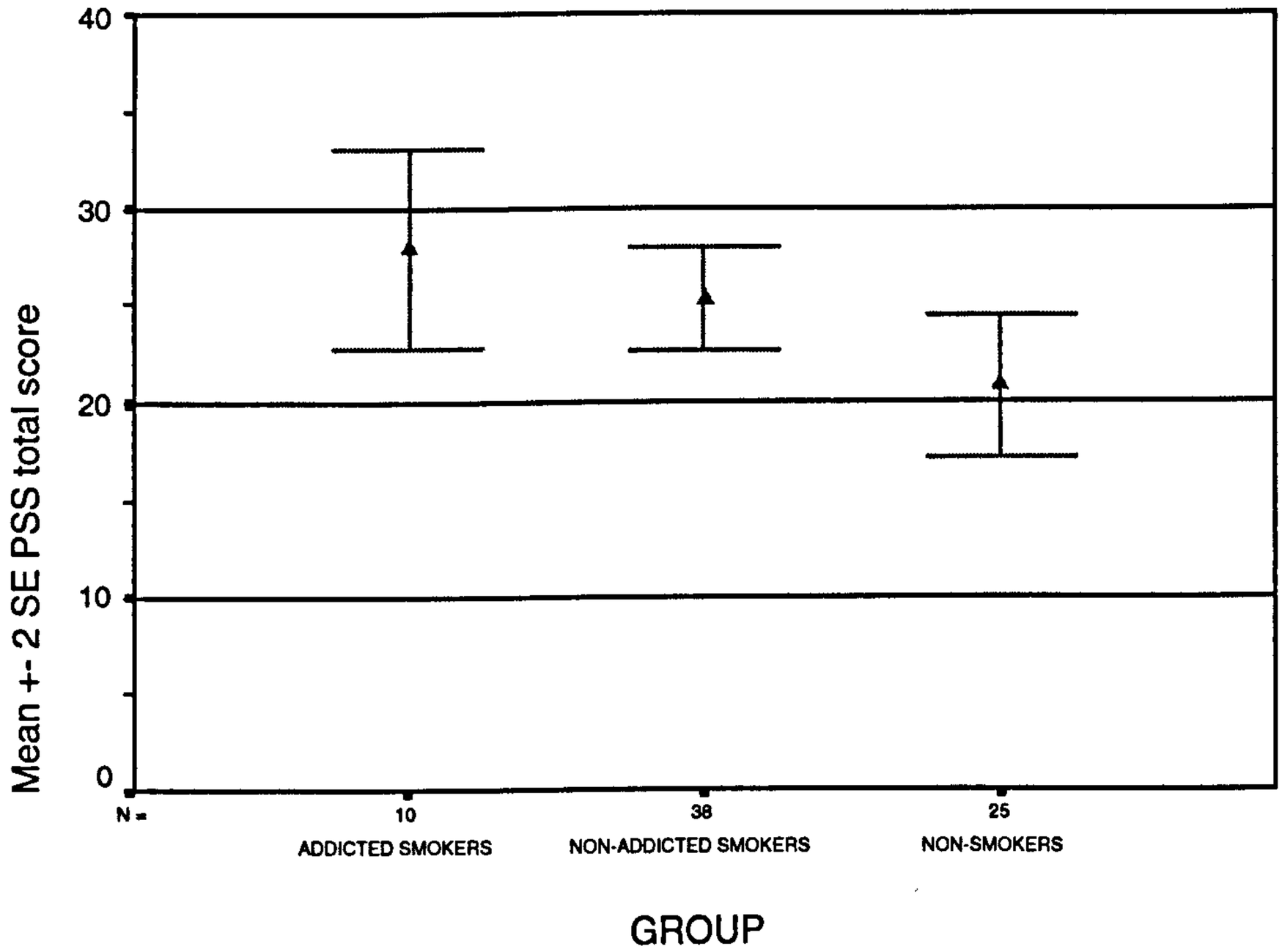


Figure 5.2 **Error-bar graph showing mean 'Health Confidence' factor scores (from Health Orientation Scale) for non-smokers, addicted and non-addicted smokers.** (For details see legend to Figure 5.1)

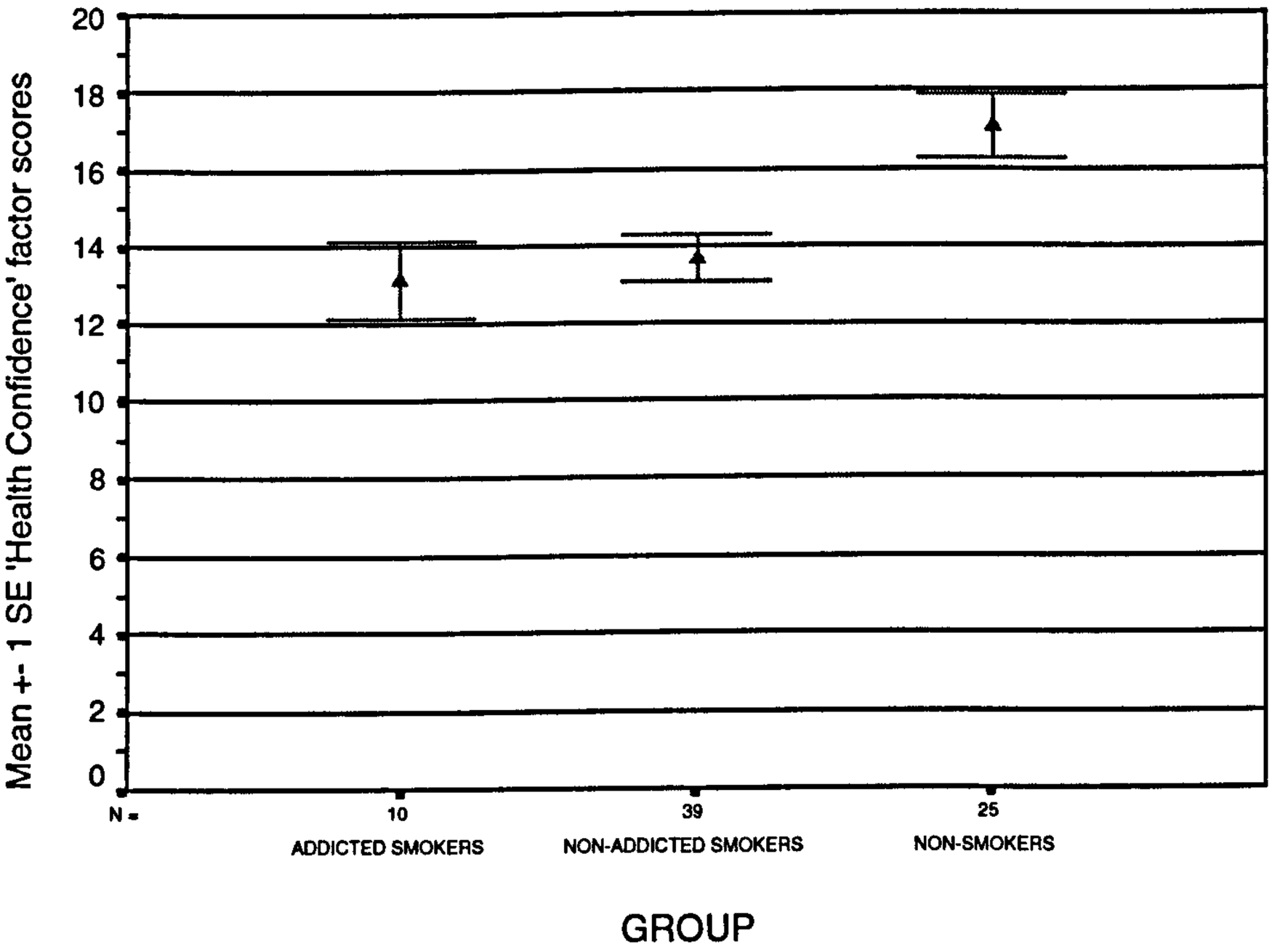


Figure 5.3 **Error-bar graph showing mean 'Motivation to not be unhealthy' factor scores (from Health Orientation Scale) for non-smokers, addicted and non-addicted smokers.** (For details see legend to Figure 5.1)

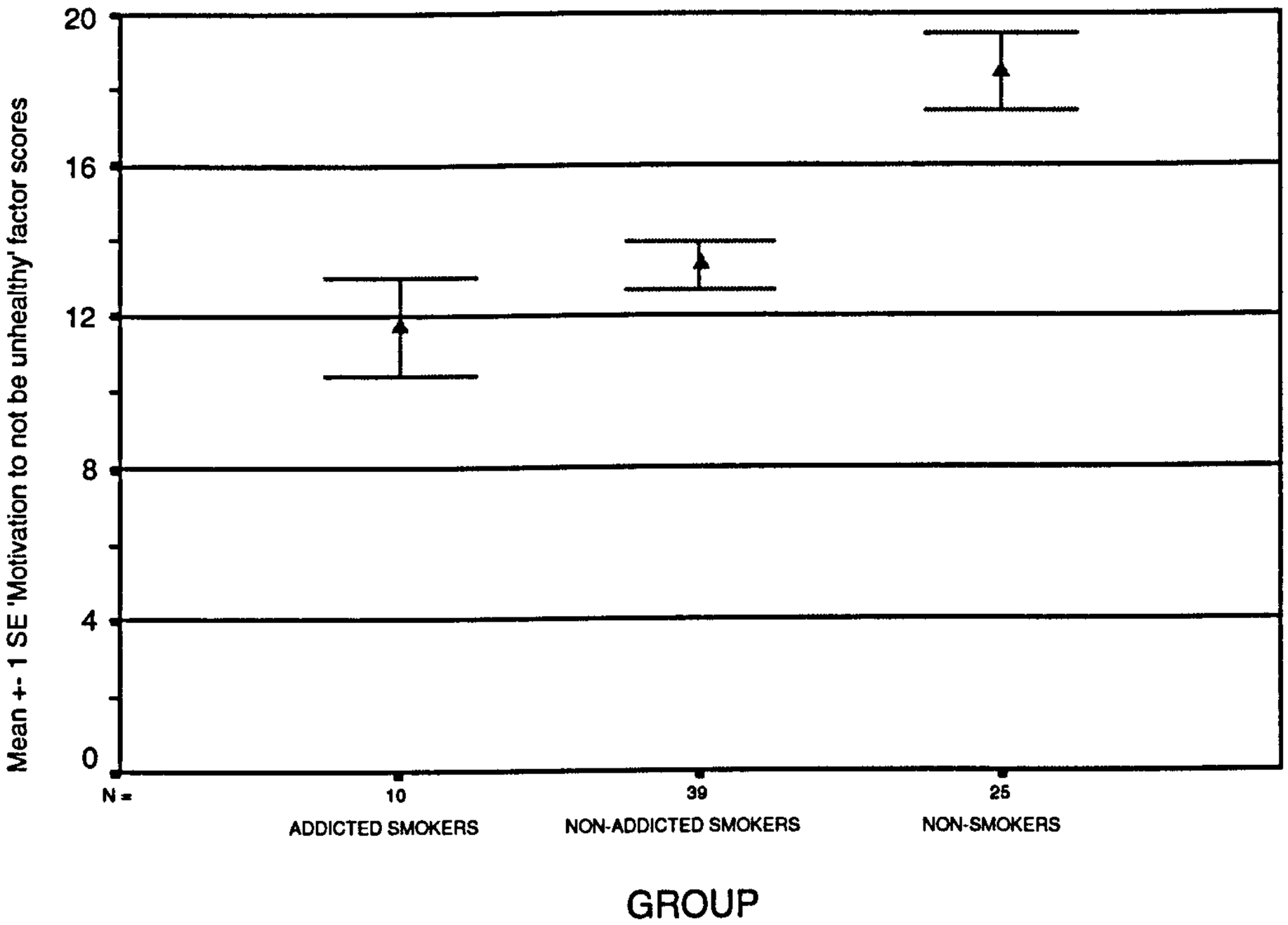


Figure 5.4 **Error-bar graph showing mean 'Motivation to be healthy' factor scores (from Health Orientation Scale) for non-smokers, addicted and non-addicted smokers.** (For details see legend to Figure 5.1)

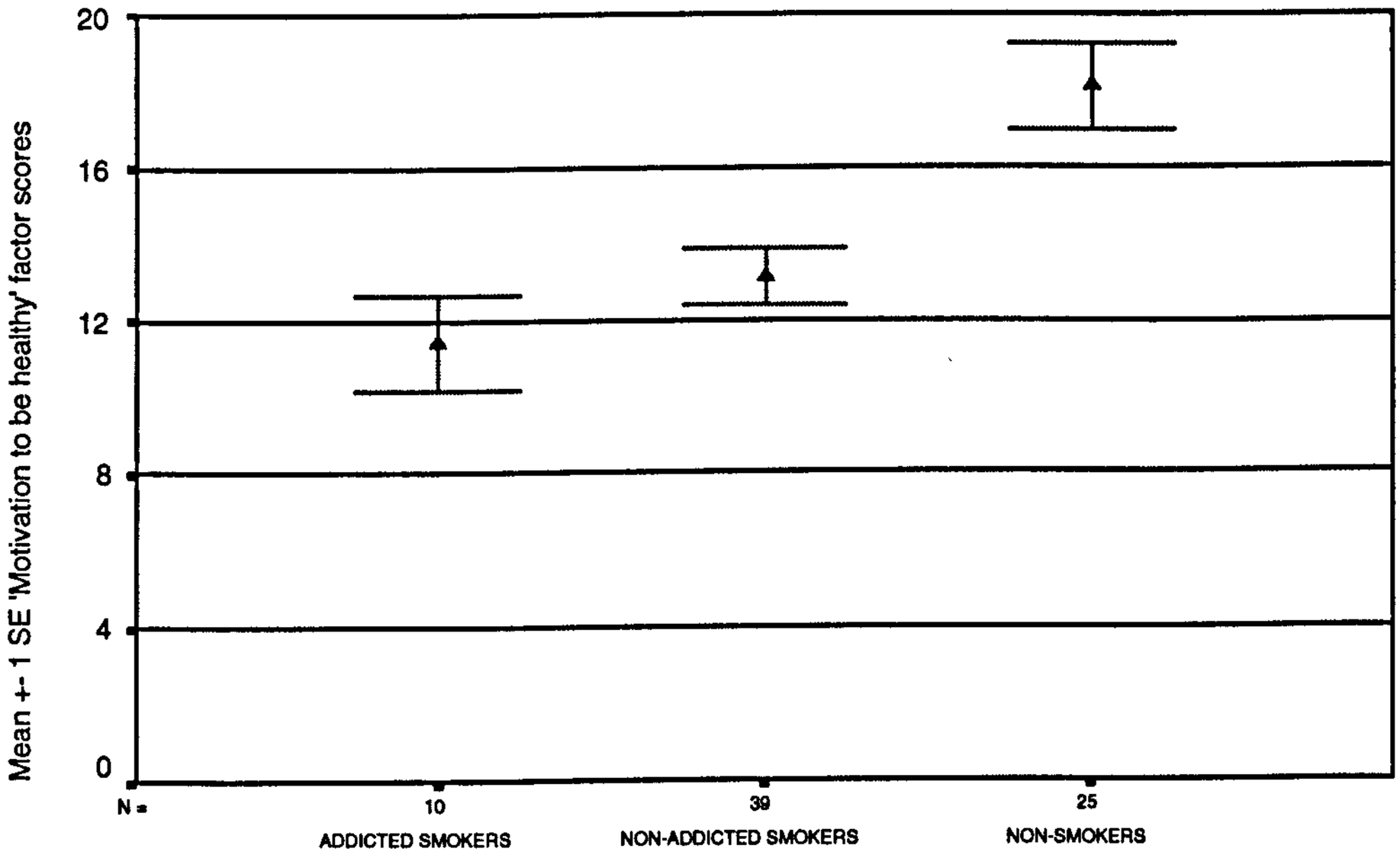


Figure 5.5 **Error-bar graph showing mean Cognitive Failure Questionnaire scores for non-smokers, addicted and non-addicted smokers.** (For details see legend to Figure 5.1)

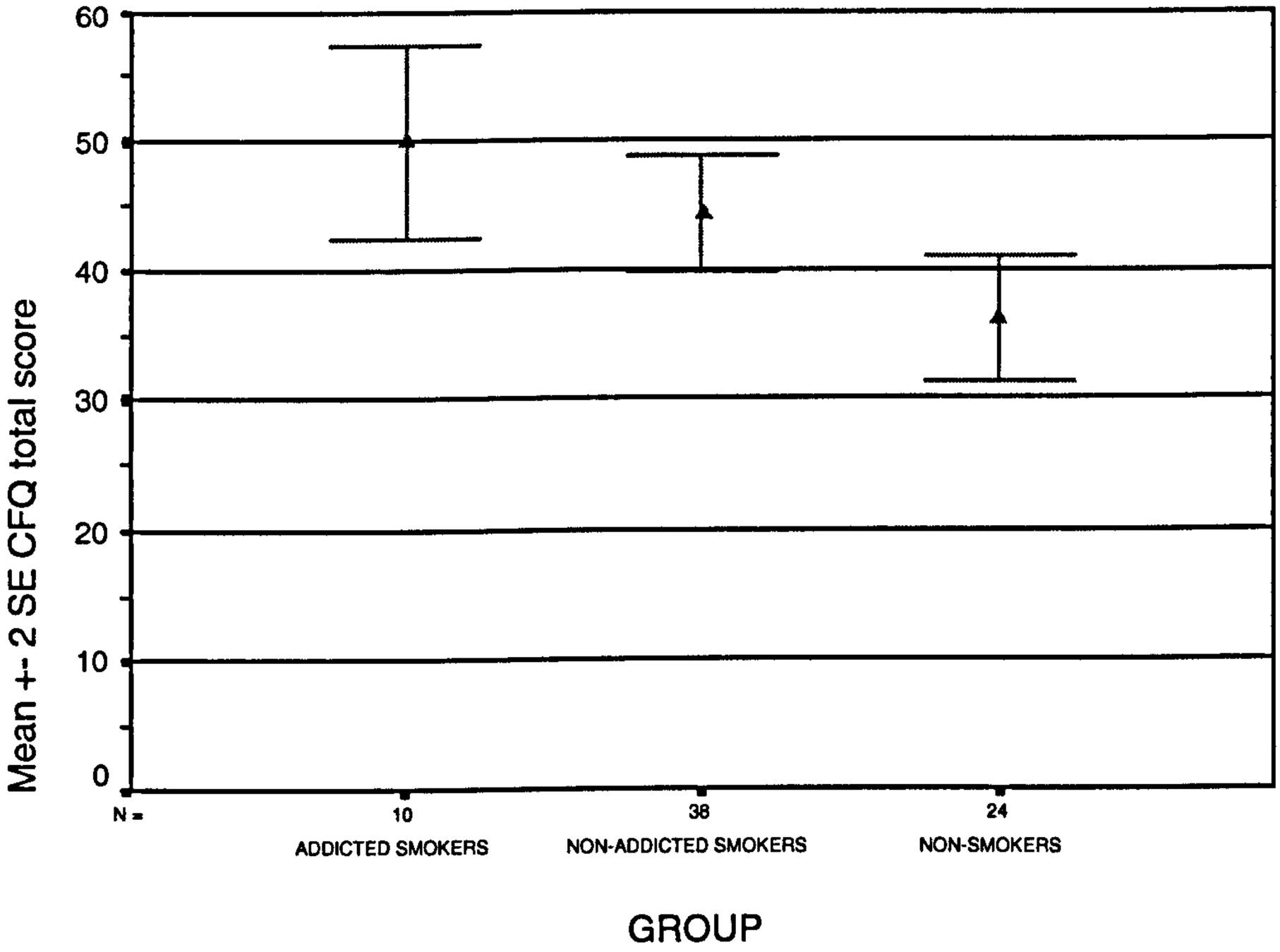


Figure 5.6 **Error-bar graph showing mean Middlesex Hospital Questionnaire Anxiety factor scores for non-smokers, addicted and non-addicted smokers.** (For details see legend to Figure 5.1)

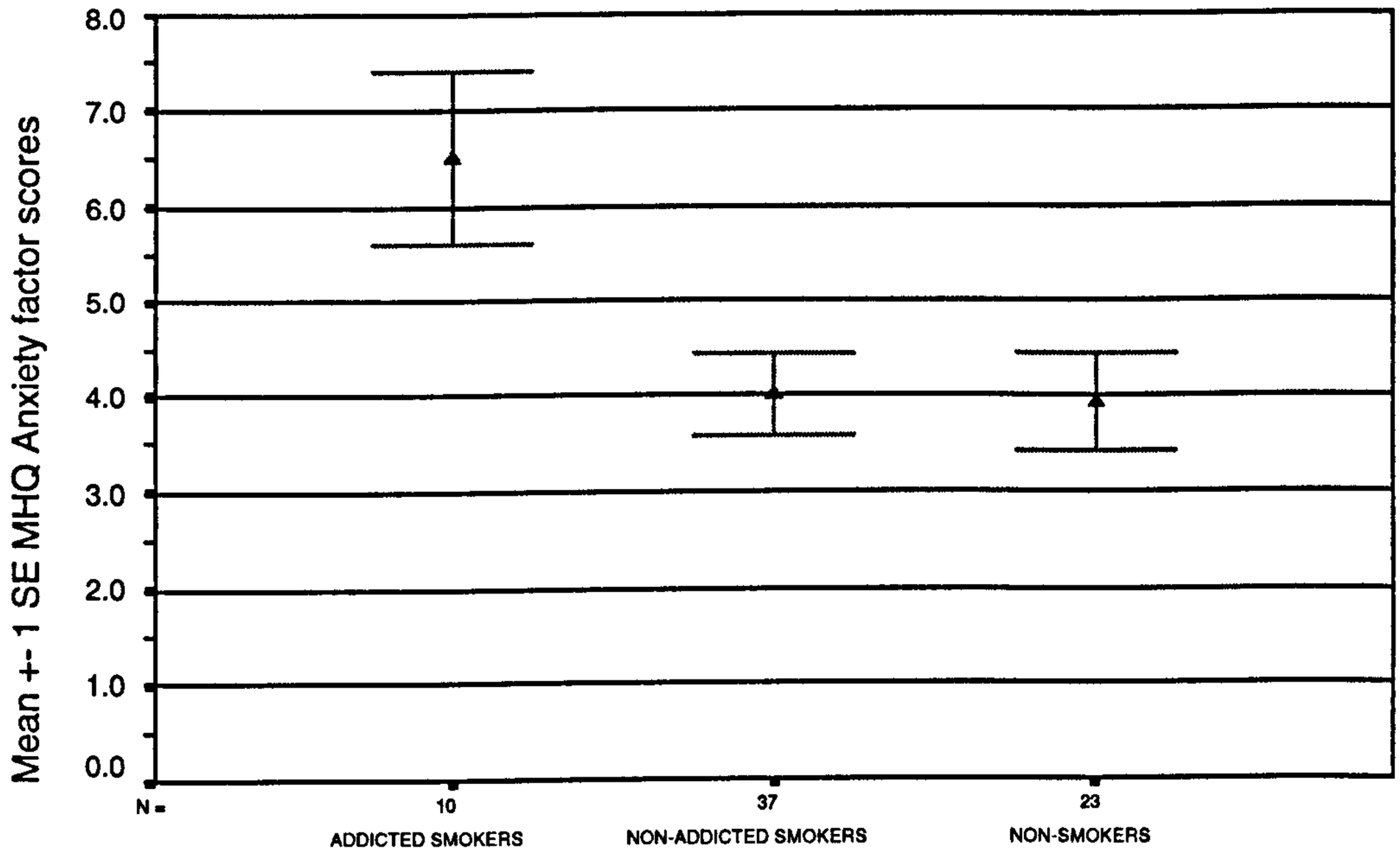


Figure 5.7 Error-bar graph showing mean Middlesex Hospital Questionnaire Depression factor scores for non-smokers, addicted and non-addicted smokers. (For details see legend to Figure 5.1)

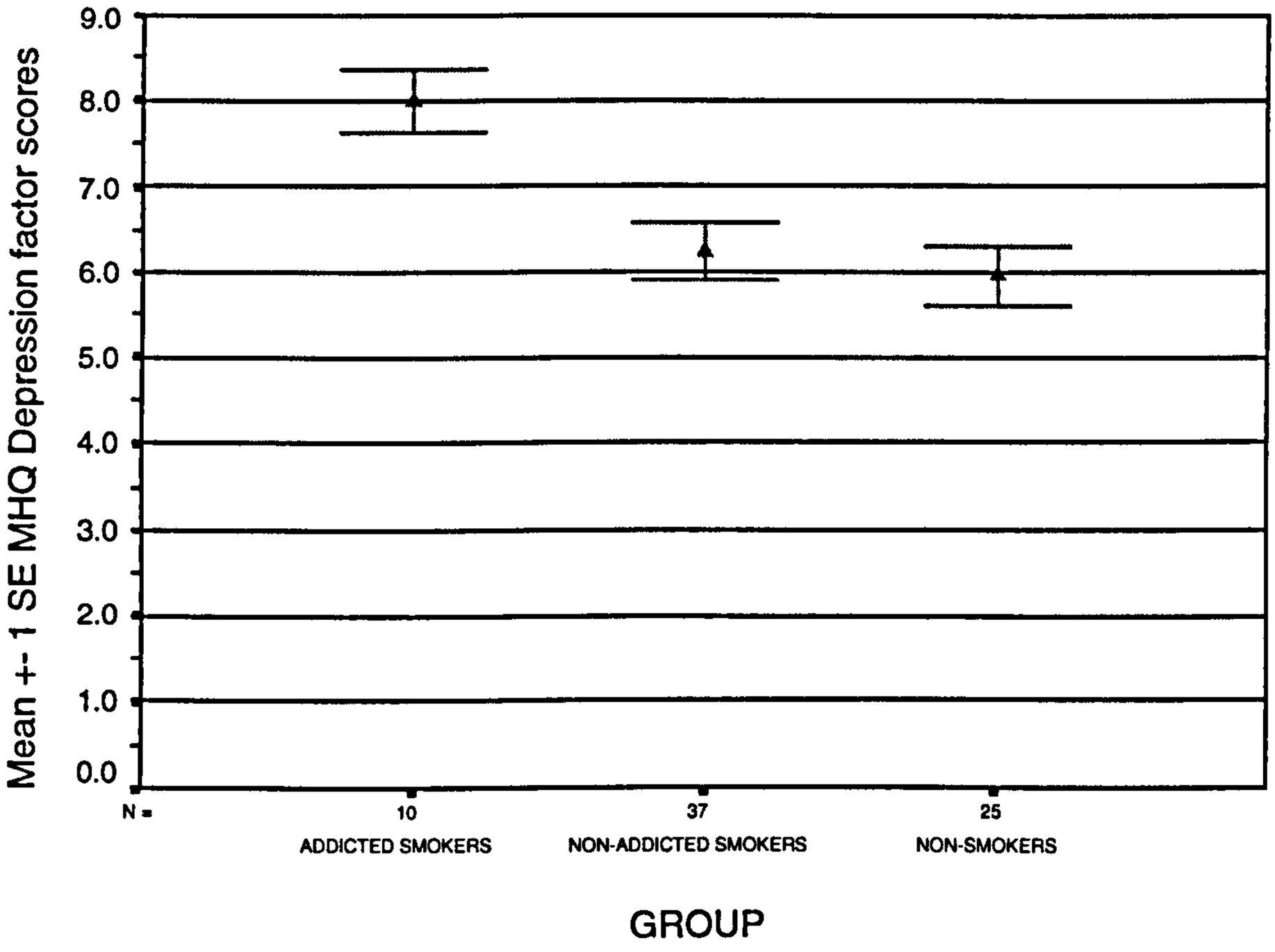


Figure 5.8 Scatterplot showing relationship between level of tobacco dependence (Addiction Index score) and MHQ Depression factor scores for addicted and non-addicted smokers (outlier removed).

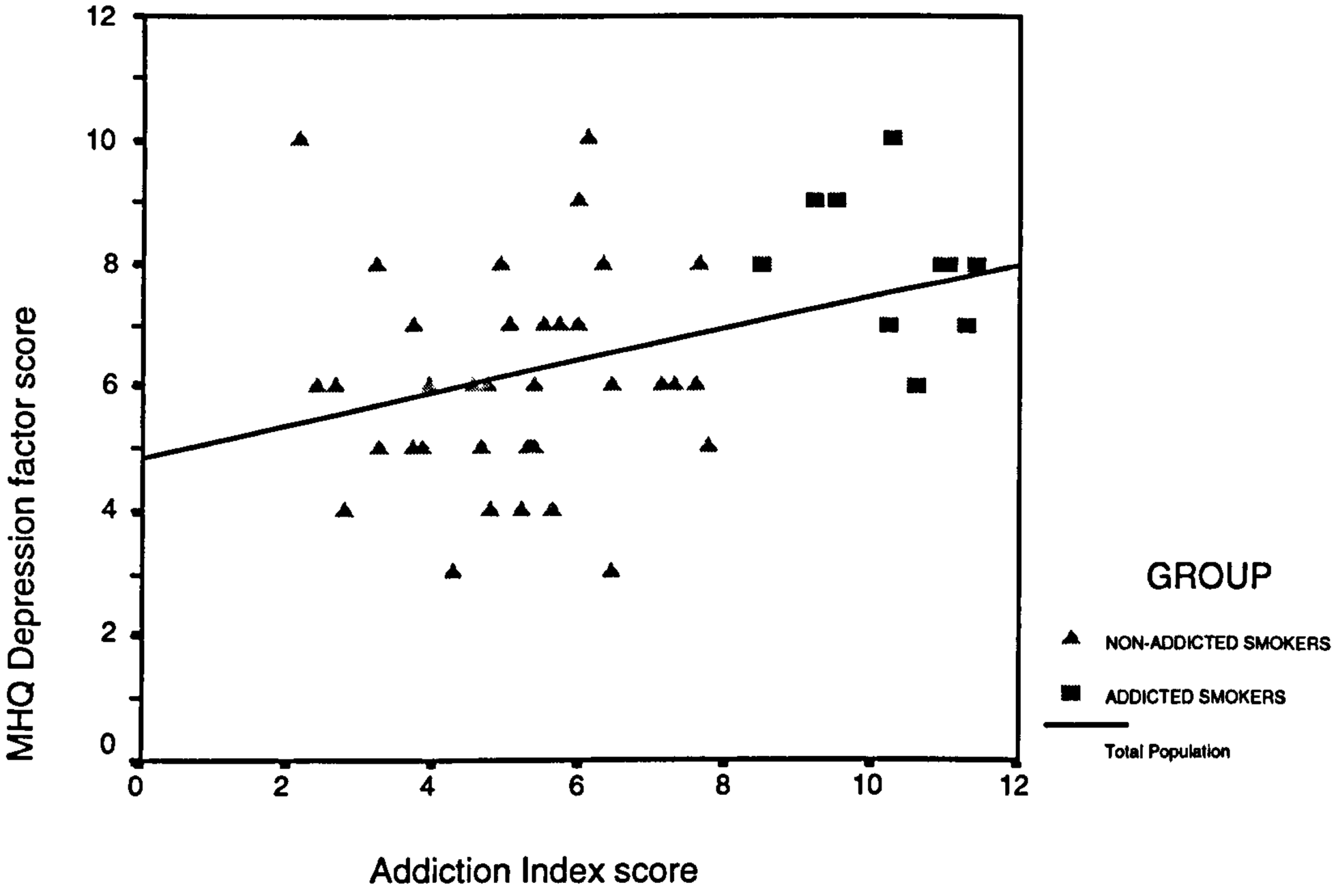


Table 5.1 Psychosocial scores for non-smokers, addicted and non-addicted smokers on the instruments used in the questionnaire battery.

VARIABLE	ADDICTED SMOKERS	NON-ADDICTED SMOKERS	NON-SMOKERS	F-RATIO‡
ISEL – Appraised support	33.50 (6.04)	32.38 (5.42)	32.46 (3.75)	0.20
ISEL – Tangible support	31.80 (4.94)	32.15 (4.79)	33.52 (3.12)	0.88
ISEL – Self-esteem support	28.80 (4.37)	29.30 (4.45)	31.91 (2-91)	3.64*
ISEL – Belonging	33.60 (3.98)	33.10 (4.66)	34.50 (3.12)	0.85
ISEL – Total score	127.70 (16.53)	127.59 (16.82)	132.82 (9.76)	0.91
SNI – Total score	9.56 (1.81)	10.36 (3.13)	9.31 (2.80)	0.97
UCLA Loneliness	26.40 (12.29)	28.78 (12.97)	26.04 (12.66)	0.39
Self-Esteem	59.20 (15.76)	57.67 (13.50)	63.52 (11.06)	1.42
SRI – Control (Personal)	30.30 (8.17)	31.79 (5.07)	35.25 (5.31)	3.86*
SRI – Control (Interpers.)	32.20 (9.04)	31.82 (7.85)	34.08 (7.03)	0.66
Life Events (Negative)	3.90 (2.33)	2.97 (2.85)	2.00 (1.66)	2.45
Life Events (Positive)	1.60 (0.97)	1.69 (1.52)	1.56 (1.16)	0.08
Life Events (Total)	5.50 (2.07)	4.67 (3.56)	3.56 (2.33)	1.77
Perceived Stress Scale	27.90 (8.14)	25.24 (8.13)	20.76 (8.73)	3.30*
HOS – Health Confidence	13.10 (3.21)	13.67 (3.88)	17.08 (4.20)	6.80***
HOS – Health Anxiety	12.00 (4.08)	12.38 (4.33)	9.58 (3.91)	3.47*
HOS – Motivation Healthy	11.4 (3.92)	13.13. (4.78)	18.08 (5.07)	9.93***
HOS – Motiv. Unhealthy	11.70 (4.03)	13.31 (4.16)	18.44 (5.13)	12.72***
HOS – Health Consc'ness	15.80 (3.33)	15.90 (3.07)	18.04 (4.42)	2.30
Cognitive Failures Q'naire	49.90 (11.87)	44.37 (13.83)	36.08 (12.00)	4.93**
MHQ – Anxiety	6.50 (2.84)	4.00 (2.65)	3.91 (2.45)	4.05*
MHQ – Somatic symptoms	5.10 (2.81)	3.86 (2.04)	4.20 (2.29)	1.20
MHQ – Depression	8.00 (1.15)	6.24 (2.05)	5.96 (1.72)	4.63*
MHQ – Obsessive sympts.	3.10 (1.37)	2.68 (1.62)	2.56 (1.66)	0.41
MHQ – Obsessive Pers'ty	2.00 (1.25)	2.00 (1.13)	2.64 (1.25)	2.36
CHIPS – Physical sympts.	6.40 (6.98)	6.50 (5.34)	5.64 (5.47)	0.18
Symptoms Checklist Total	3.56 (4.07)	4.29 (2.84)	2.36 (2.29)	3.34*

‡ - treatment df=2, error degrees of freedom are variable (between 66 and 71)
*- significant at p<.05 level, **- significant at p<.01 level, ***- significant at p<.001 level

Chapter 6 – Craving and withdrawal symptoms after 24-hour abstinence and the effect of reinstatement through *ad libitum* smoking

6.1 Introduction

Nicotine is regarded as a powerfully addictive substance. Traditional models of drug dependence and drug motivation have accorded withdrawal a central role in motivating addictive drug use and relapse (Isbell & White, 1953; Seevers, 1962; Wikler 1973). Despite withdrawal symptoms not being a universal consequence of abstinence, most smokers experience withdrawal symptoms and tobacco cravings on cessation (Hatsukami et al. 1985; Shiffman, 1979). The mechanisms by which abstinence from smoking induces withdrawal symptoms are not well understood. Withdrawal phenomena may be due to pharmacological dependence on nicotine similar to dependence observed with other drugs of abuse (Shiffman, 1979; Hatsukami, Hughes & Pickens, 1985).

The severity of the withdrawal syndrome is variable, with some smokers appearing to suffer very little, while others experience distressing symptoms. It would be expected for heavier smokers to experience greater withdrawal discomfort: however, usual daily cigarette consumption has not been reliably shown to predict severity of withdrawal. Studies have shown that smokers with a high pre-abstinence nicotine intake experience the greatest discomfort (Burns, 1969; West & Russell, 1985). Hughes & Hatsukami (1986) and Pomerleau et al. (1983b) both reported that subjects

who were more tolerant had more withdrawal discomfort. The latter results are consistent with earlier theories (e.g. Kalant, LeBlanc & Gibbins, 1971) postulating that tolerance and withdrawal develop concomitantly because they are both manifestations of the development of physical dependence. Hughes & Hatsukami (1986) also found that withdrawal effects were initially the opposite of nicotine effects, then decreased towards baseline; a "rebound" phenomenon consistent with opiate/sedative type dependence. Perhaps most saliently, administration of nicotine relieves tobacco withdrawal (e.g. Hughes et al. 1984; Hughes & Hatsukami, 1985).

Shiffman (1979) purports that dose dependency is so characteristic of withdrawal syndromes from other substances that establishing this effect for tobacco would be an important step in understanding nicotine dependence. Seven symptoms have been collated and termed *tobacco withdrawal* in DSM-IV: craving for tobacco, irritability, anxiety, difficulty concentrating, restlessness, headaches, drowsiness, and gastrointestinal tract disturbances. Shiffman (1979) reports that the onset of withdrawal prompts smoking, deters attempts to stop smoking, reduces cessation success and causes relapse to smoking.

Various studies have described tobacco withdrawal phenomena, although the validity and generalisability of these reports is contentious. Many of these studies relied on self-reported symptoms that may have been more dependent on subjectivity, although others have also utilised objective measures (Hughes & Hatsukami, 1986). Nonetheless, several laboratory experiments have demonstrated objective changes analogous with self-reported withdrawal symptoms. Concerns exist regarding a

"rationalisation bias" whereby abstinent smokers exaggerate withdrawal symptoms in order to rationalise their (actual or potential) inability to quit.

DSM-IV incorporates increased anxiety as one of the nicotine withdrawal symptoms. Most studies report a transient increase in anxiety during abstinence (Hughes, Higgins & Bickel, 1994). West & Hajek (1997) showed that 24-hour abstinence produced no increased anxiety, and argued that it is not a robust element of the tobacco withdrawal syndrome. Some studies show a decrease in anxiety below pre-cessation levels after several weeks of abstinence (Gross & Stitzer, 1989). Population studies present data that smokers report higher anxiety levels than individuals who have never smoked or ex-smokers (Jarvis, 1994).

Aside from craving, daytime sleepiness, difficulty sleeping at night and irritability (which may impact on sleep patterns) are the most frequently reported symptoms of tobacco withdrawal, occurring in up to 70% of those who stop smoking (Hatsukami et al. 1985; 1988). Hughes & Hatsukami (1986) stated that more than half of their sample reported decreased adequacy of sleep and decreased time asleep. Prosise et al. (1994) report significant increases in number of relative arousals, sleep stage changes and awakenings during smoking cessation. Hughes, Higgins & Hatsukami (1990) claim that abstinence appears to increase the number of awakenings and the amount of REM sleep, although these effects cannot be categorically ascribed to nicotine deprivation. This suggests that changes in sleep or sleep-associated variables may be a core problem in smoking cessation.

West & Schneider (1987) describe craving as "potentially the most important feature of cigarette withdrawal", however there is little consensus concerning a definition of craving. The United Nations International Drug Control Programme (UNDCP) and World Health Organisation (WHO) jointly presented a definition of drug craving as "the desire to experience the effect(s) of a previously experienced psychoactive substance". It is widely accepted that craving contributes significantly to the development and maintenance of drug dependence. The DSM-IV states that craving is "likely to be experienced by most if not all individuals with substance dependence". Shiffman (2000) argues that it currently seems most useful to regard craving as a subjective motivational state.

Craving is thus considered analogous to emotions, and to have motivational significance for an individual. It is also considered analogous to hunger, as both craving and hunger are subjectively experienced as a need for something to be ingested (Kassel & Shiffman, 1992). Modern conceptions of craving often incorporate cognitive concepts such as cognitive labelling, outcome expectancy and cognitive processing (Tiffany, 1999). These models posit that craving is a non-automatic process (and therefore not simply emotional or motivational) that requires mental effort and is limited by a person's cognitive ability (Tiffany, 1999). Hughes & Hatsukami (1986) stated that 62% of their sample reported increased cravings for tobacco after abstinence. They included craving in their measures of withdrawal, as they were using DSM-III criteria. However, due to accounts that smokers report craving even during smoking, this item was eliminated from the tobacco withdrawal syndrome detailed in DSM-IV. It has been subsequently argued that the incidence of

craving whilst smoking may be more due to procedural issues than to true unreliability of subjective experience (Jarvik et al. 2000b).

Under conditions of deprivation, smokers report cravings for tobacco that generally translate into smoking, and increased levels of deprivation typically lead to stronger cravings (Payne et al. 1996). Cravings for cigarettes are commonly reported as motivators or precursors to actual use (Marlatt & Gordon, 1985), and are typically initiated by a variety of internal (emotions, thoughts) and external (situational) cues (Abrams et al. 1987; Niaura et al. 1992, 1998; Shiffman et al. 1996). Cravings reliably predict relapse to cigarettes (Killen & Fortman, 1997; Shiffman et al. 1997) and precipitate lapses following abstinence (Shiffman et al. 1996). Early research found no difference in craving between light and heavy smokers following 48-hour abstinence (Gritz & Jarvik, 1973).

Since it is accepted as a subjective state, self-report measures dominate assessment and measuring of craving. Although other measurement modalities have been suggested, these measures often lack specificity as they are under control of numerous other influences. Shiffman (2000) purports that although objective measures of craving might be developed in future, subjective self-report appears to be the only viable current option. As with other reported withdrawal symptoms, this presents its own problems, such as interpretation of the questions and/or terms used, social demand and self-deception, but these are partially overcome by use of repeated measures designs since these issues will often control for themselves.

Tiffany & Drobes (1991) Questionnaire of Smoking Urges is an example of a multi-dimensional subjective self-report tool measuring cravings for smoking. Its two-factor structure allows subjects to rate their desire to smoke based on expected positive reward and appetitive desire to smoke (positive reinforcement), and removal of withdrawal and/or negative affect (negative reinforcement).

Tobacco "chippers" are characterised as regular but non-dependent smokers, and have been shown to exhibit no significant signs or symptoms of withdrawal after overnight abstinence (Shiffman, 1989). This is consistent with reports that claim that chippers easily and voluntarily abstain from smoking for a day or more each week. The behaviour of this group challenges conventional notions regarding addiction and its causes, as chippers chronically expose themselves to an addictive drug yet show no evidence of dependence. Chippers may have low nicotine tolerance, hence the absence of a withdrawal syndrome. This is likely to assist this group in avoiding tobacco dependence, although little else is known about the factors defining these individuals and protecting them from developing addiction to smoking.

The current study aimed to demonstrate that 24-hour abstinence from tobacco would cause subjects to rate withdrawal symptoms and urges to smoke significantly greater than when non-deprived, and that these would be reversed by 45 minutes of *ad libitum* smoking. It was predicted these effects would be more marked in addicted smokers than non-addicted smokers. This could provide a useful way of characterising the presence or level of nicotine dependence.

Hypotheses:

I. that 24-hour abstinence will increase urges to smoke and reported severity of withdrawal symptoms in all smoking subjects.

II. that overall changes of withdrawal symptom ratings between baseline and withdrawn sessions will be correlated with nicotine dependence as indicated by addiction index scores.

III. that smoking urges measured by the QSU would be greater in withdrawn sessions in the addicted smokers group than in the non-addicted smokers.

IV. that reinstatement through 45 minutes of *ad libitum* smoking will significantly reduce withdrawal symptoms and urges to smoke in all smoking subjects.

V. that overall changes of withdrawal symptom ratings between withdrawn and reinstated sessions will be correlated with nicotine dependence as indicated by addiction index scores.

VI. that smoking urges measured by the QSU would be more reduced by reinstatement in the addicted smokers than the non-addicted smokers group.

6.2 Method

6.2.1 Design

This was a between subjects comparison of three groups (addicted smokers, non-addicted smokers and non-smoker controls) using a Withdrawal Symptoms Checklist based on Hughes & Hatsukami (1986), and Tiffany & Drobes (1991) Questionnaire of Smoking Urges.

6.2.2 Subjects

Subjects (N=75) participated as part of the mood and cognitive performance study presented in Chapter 3. The participants were categorised as non-smokers (n=25), addicted smokers (n=10) and non-addicted smokers (n=40). A full description of the subject sample and recruitment information is included in Chapters 2 and 3.

6.2.3 Questionnaires

Withdrawal Symptoms Checklist (WSC)

This is a fifteen-item checklist based on the Hughes & Hatsukami (1986) study on tobacco withdrawal. It features eight items taken from the DSM-III symptom list for the tobacco withdrawal syndrome, plus further items added by the authors. It presents each item (craving for tobacco, irritability, etc.) with 4 checkboxes labelled 0 to 3. 0=not present, 1=mild, 2=moderate, 3=severe. See Appendix XIV.

Questionnaire of Smoking Urges (QSU)

This is a 32-item questionnaire developed and validated by Tiffany & Drobes (1991).

Subjects are presented with positive or negative statements regarding urge to smoke.

Subjects were asked to indicate on a Likert-type scale how strongly they agree or disagreed with each statement. Each item was scored on a scale of 1 (strongly disagree) to 7 (strongly agree). See Appendix XV.

6.2.4 Procedure

Subjects were fully briefed on the procedure prior to starting, and were informed of their rights and requirements. Subjects were required to attend the Health Psychology Research Unit on a minimum of two occasions. Three sessions were completed: Baseline, Withdrawn and Reinstated. The latter 2 sessions were always performed consecutively.

Baseline

Subjects attended the HPRU at 9.00 am, having been instructed to:

a) Smoke *as they normally would* both in the previous evening and in the morning before attending the Unit.

b) Refrain from excessive alcohol intake (>4 units) during the previous evening.

c) Consume normal caffeine intake before attending the Unit, up to 20 minutes prior to arrival.

d) Have a typical sleep pattern during the preceding night.

e) Not exercise vigorously in the morning before attending the Unit.

On arrival, subjects were shown to a booth and asked to complete the Baseline Session Pre-test Questionnaire. This booklet contained questions regarding eating,

drinking and smoking behaviour in the last 24 hours, a Withdrawal Symptoms Checklist, and Tiffany & Drobes (1991) Questionnaire of Smoking Urges.

Withdrawn

Subjects attended the HPRU at 9.00 am, having been instructed to:

a) Smoke *nothing* in the preceding 24 hours before attending the Unit, and follow the conditions b) to e) from the Baseline session.

On arrival at the Unit, subjects were breathalysed using a carbon monoxide breathalyser to ascertain whether they had complied with the 24-hour abstinence protocol. If the breathalyser registered less than 10 PPM (parts per million) CO count, the subject was allowed to continue with the experiment. Subjects were also asked to report if they had smoked during the designated abstinence period. These details were recorded.

Subjects were shown to their testing booth and asked to complete the Withdrawn Session Pre-test Questionnaire (see Section 6.2.4). This booklet consisted of questions regarding eating, drinking and smoking behaviour in the last 24 hours, a withdrawal symptoms checklist, Tiffany & Drobes (1991) Questionnaire of Smoking Urges.

Upon completion of the computer tests by all participants in the laboratory, subjects were informed they had an hour before the final session. They were issued with ashtrays and advised that they could smoke at least 1 cigarette during the next 45 minutes. Subjects smoked between 1 and 5 cigarettes. During this hour "break",

subjects were administered Cloninger et al.'s (1993) Temperament & Character Inventory (see Chapter 4). No caffeine or eating was permitted during this period, and subjects generally passed time reading. After 45 minutes, subjects were asked to extinguish any cigarettes and relax. The final fifteen minutes were smoke-free in order to avoid direct cognitive effects of nicotine. Once the hour break was concluded, the next session commenced.

Reinstated

Subjects then completed the Reinstated Session Pre-test Questionnaire. This booklet consisted of questions regarding eating, drinking and smoking behaviour in the last hour, a withdrawal symptoms checklist, Tiffany & Drobes (1991) Questionnaire of Smoking Urges. Once these were completed, subjects were asked to leave their booklets open on the final page, which was a response sheet for the Free Recall memory task.

6.3 Results

6.3.1 Effects of abstinence on smokers' withdrawal symptom ratings

Baseline session total WSC ratings were compared with the withdrawn session total WSC ratings using repeated measures analysis of variance. Smoking group was the between-subjects factor. Mean WSC ratings for the groups in each session are shown in Table 6.1.

There was a significant interaction between WSC total ratings and smoking group ($F\{2,68\}=7.88$, $p<.001$). Tukey post-hoc analysis showed that both addicted and non-

addicted smokers increased their ratings in withdrawal relative to non-smokers (both contrasts $p<.001$) (see Figure 6.1, Table 6.2). No significant differences were shown between the two groups of smokers.

Further analyses were performed on individual WSC items ratings (see Table 6.1) to identify symptom differences between the addicted and non-addicted smoker groups. Baseline and withdrawn sessions were compared, using repeated measures analysis of variance with Tukey post-hoc analysis. A significant interaction effect between session and smoking group was shown for craving for tobacco ($F\{2,70\}=11.21$, $p<.001$). Tukey post-hoc analysis demonstrated addicted smokers reported greater increases in craving for tobacco than non-addicted smokers in withdrawn sessions compared to baseline ($p<.025$) (Figure 6.2, Table 6.3).

6.3.2 Relationship between withdrawal sensitivity and tobacco dependence

Change scores were computed to present how total withdrawal symptomatology had changed from Baseline (non-deprived) to Withdrawn session (post-24-hour abstinence), i.e. Withdrawn WSC total minus Baseline WSC total. Change scores were also computed for the individual items in WSC (Withdrawn WSC item minus Baseline WSC item). Data from non-smokers were excluded from these analyses. Since the data was non-parametric, a series of Spearman's Rho analyses was used to investigate correlations between addiction index scores and withdrawal change scores.

Significance levels were 1-tailed due to the predicted directionality of the correlations. Addiction index correlated positively with total WSC change score ($r=0.282$, $p<.05$ 1-

tailed). This showed that subjects with higher addiction scores experienced greater increases in the overall withdrawal symptoms measured (Figure 6.3).

Addiction index correlated positively with individual WSC change scores for the "restlessness" ($r=0.255$, $p<.05$ 1-tailed) and "sleep disturbance" ($r=0.274$, $p<.05$ 1-tailed) symptoms. This showed that subjects with higher addiction scores experienced greater increases in these symptoms following 24-hour withdrawal.

6.3.3 Differences between addicted and non-addicted smokers urges to smoke following 24-hour abstinence

Baseline session QSU Factor 1 scores were compared with the withdrawn session QSU Factor 1 scores using repeated measures analysis of variance. Smoking group was the between-subjects factor. Non-smokers were excluded from these analyses.

All smoking subjects were shown to increase QSU Factor 1 (urges relating to positive reinforcement) scores following 24-hour withdrawal ($F\{1,48\}=44.76$, $p<.001$), however there was no interaction between smoking group and these scores. Although addicted smokers rated their Factor 1 urges to smoke in withdrawal higher than non-addicted smokers, this difference was not significant (Table 6.4, Figure 6.4).

Although all smokers had increased QSU Factor 2 (urges relating to negative reinforcement) scores following 24-hour withdrawal ($F\{1,48\}=29.56$, $p<.001$), there was no interaction between smoking group and these scores. Addicted smokers rated

their Factor 2 urges to smoke much higher in withdrawal than non-addicted smokers, however this difference was not significant (Table 6.5, Figure 6.4).

Although the QSU was not shown to discriminate between the addicted and non-addicted groups, it is relevant to and affected by levels of dependence. Change scores were computed to characterise the difference between baseline session and withdrawn session for both QSU Factors (Withdrawn QSU Factor 1 scores minus Baseline QSU Factor 1 scores, and same for Factor 2). These change scores were then correlated with Addiction Index scores using Spearman's Rho. Significance levels were 1-tailed due to the predicted directionality of the correlations. Although there was no significant correlation for Factor 1 change scores, levels of nicotine dependence (Addiction Index) were positively correlated with urges to smoke relating to negative reinforcement (Factor 2 change scores) ($r=0.245$, $p<.05$ 1-tailed; see Figure 6.5.).

6.3.4 Effects of reinstatement on smokers' withdrawal symptom ratings

Withdrawn session total WSC ratings were compared with the Reinstated session total WSC ratings using repeated measures analysis of variance. Smoking group was the between-subjects factor, and Baseline session WSC ratings were included as a covariate in the analysis to act as a quantitative predictor.

There was a significant interaction between WSC total ratings and smoking group ($F\{2,67\}=4.87$, $p<.025$). Pairwise comparisons of means showed that both addicted and non-addicted smokers increased their ratings in withdrawal relative to non-

smokers (both contrasts p<.001) (see Figure 6.6, Table 6.2). No significant differences were shown between the two groups of smokers.

Further analyses were performed on individual WSC items ratings (see Table 6.1) to identify symptom differences between the addicted and non-addicted smoker groups. Withdrawn and reinstated sessions were compared, using repeated measures analysis of variance with Tukey post-hoc analysis. No significant interactions between session and smoking group were shown for any of the individual WSC items, demonstrating that no particular withdrawal symptom is differentially affected by reinstatement between addicted and non-addicted smokers.

6.3.5 Relationship between reinstatement sensitivity and tobacco dependence

Change scores were computed to present how total withdrawal symptomatology had changed following reinstatement (i.e. Withdrawn (post-24-hour abstinence) WSC scores minus Reinstated (post-45-minute *ad libitum* smoking) WSC scores. Change scores were also computed in the same way for the individual items in the WSC. Data from non-smokers were excluded from these analyses. Since the data was non-parametric, a series of Spearman's Rho analyses was used to investigate correlations between Addiction Index scores and withdrawal change scores.

Addiction Index correlated negatively with total WSC change score (r=-0.27, p<.05 1-tailed) showing that subjects with higher addiction scores (tobacco dependence) experienced greater reductions in the overall withdrawal symptoms measured following 45 minutes of *ad libitum* smoking (Figure 6.7).

Addiction Index correlated negatively with individual WSC change scores for craving for tobacco symptoms ($r=-0.317$, $p<.025$ 1-tailed) showing that subjects with higher addiction scores experienced greater reductions in craving following 45 minutes of *ad libitum* smoking.

6.3.6 Differences between addicted and non-addicted smokers urges to smoke following reinstatement

Withdrawn session QSU Factor 1 scores were compared with the reinstated session QSU Factor 1 scores using repeated measures analysis of variance. Smoking group was the between-subjects factor. This analysis was repeated with Factor 2 scores. Baseline Factor scores were used as a covariate in the analysis to act as a quantitative predictor. Non-smokers were excluded from these analyses.

Although all smoking subjects were shown to have reduced QSU Factor 1 scores following reinstatement (increased primary intention and appetitive desire to smoke) ($F\{1,47\}=34.28$, $p<.001$), there was no significant interaction between smoking group and Factor 1 scores. Thus although following reinstatement non-addicted smokers reduced their ratings of Factor 1 urges to smoke more than addicted smokers, this difference was not significant (Table 6.4, Figure 6.4).

Similarly, although all smoking subjects were shown to have reduced QSU Factor 2 scores following reinstatement (decreased desire to alleviate withdrawal and reduce negative affect through smoking) ($F\{1,48\}=4.5$, $p<.05$), there was no significant interaction between smoking group and Factor 2 scores. Thus, although following

reinstatement, addicted smokers reduced their Factor 2 scores more than non-addicted smokers, this difference was not significant (Table 6.5, Figure 6.4).

Change scores were computed to characterise the difference between withdrawn session and reinstated session for both QSU Factors (Reinstated QSU Factor 1 scores minus Withdrawn QSU Factor 1 scores, and same for Factor 2). These change scores were then correlated with Addiction Index scores using Spearman's Rho, to examine whether the impact of reinstatement on smoking urges was related to level of dependence. There were no significant correlations for higher levels of nicotine dependence (Addiction Index) with Factor 1 or Factor 2 change scores quantifying reinstatement from 45-minutes *ad libitum* smoking.

6.2 Discussion

Acute 24-hour abstinence from smoking was shown to bring about an array of symptoms concordant with previous formulations of the tobacco withdrawal syndrome (e.g. Hughes & Hatsukami, 1986). Furthermore it was shown that addicted smokers reported greater "craving for tobacco" than non-addicted smokers, and that higher levels of tobacco dependence were correlated with larger increases in withdrawal symptomatology (especially "restlessness" and "sleep disturbance"). All smokers were observed to increase their ratings of urges to smoke relating to both positive and negative reinforcement (see Figure 6.4), with the latter motivation being more greatly increased in those with higher levels of tobacco dependence as measured by Addiction Index scores ($p<.05$).

Ad libitum smoking for 45 minutes (reinstatement) was shown to reverse many of these withdrawal effects; all smokers' total withdrawal symptoms were reduced, with more tobacco dependent smokers showing the greatest reductions in symptomatology (particularly "craving for tobacco"). Reinstatement also elicited significant reductions in smokers urges to smoke pertaining to both positive and negative reinforcement, and these reductions were independent of levels of tobacco dependence and smoker sub-group.

The Withdrawal Symptoms Checklist (adapted from Hughes & Hatsukami, 1986) was shown to be a sensitive tool for measuring levels of tobacco withdrawal. All smokers reported significant increases in total withdrawal symptom severity, concordant with Hughes & Hatsukami's (1986) findings. No differences were shown between addicted and non-addicted smokers in the total symptom severity response to withdrawal. This finding is not in accord with Shiffman (1989), whose chippers showed significantly fewer symptoms than dependent smokers after overnight abstinence. This indicates tangible differences between "chippers" and "non-addicted smokers". The latter group is clearly less stringent and includes smokers with moderate levels of tobacco dependence. These individuals are likely to experience significant withdrawal symptoms.

Individual WSC items were examined in order to elucidate withdrawal symptoms that could discriminate addicted and non-addicted smoker groups. "Craving for tobacco" was more increased by withdrawal in the addicted smokers than the non-addicted smokers. This finding is concordant with Shiffman (1989), who reported that "Desire

to Smoke" (a factor on the Shiffman & Jarvik (1976) withdrawal scale) was significantly greater in dependent smokers than chippers following overnight abstinence. These findings support the grouping methodology used in this research (see Chapter 2). However, it is possible that a contingent of the non-addicted group may be moderately tobacco dependent, or may go on to develop greater dependence.

When dependence is quantified on a continuous scale (Addiction Index, see Chapter 2), it was demonstrated that higher scores were correlated with greater increases in symptom severity (total WSC ratings) following abstinence. These findings support previous research showing a similar correlation between "Dependent" factor scores on Russell et al.'s (1974) Smoking Motivation Questionnaire (SMQ) and overall withdrawal severity (West & Russell, 1985). Of the individual WSC items examined, "sleep disturbance" and "restlessness" ratings were positively correlated with Addiction Index. These findings are interesting, as they suggest that when nicotine levels are lowered through abstinence, dependent smokers have trouble relaxing or "switching off". Results of previous studies are consistent with the finding that dependent smokers have disturbed sleep following abstinence (e.g. Hughes & Hatsukami, 1986; Prosise et al. 1994), and rate restlessness as increased (Hughes & Hatsukami, 1986).

West & Russell (1985) showed no correlation between "restlessness" ratings and "Dependent" factor scores on the SMQ. Closer observation of their results showed they used 2-tailed Spearman's Rho to analyse their correlations. If West & Russell's (1985) hypotheses had been directional they could have used a 1-tailed test, and the

correlation (r=0.30) would have been significant at the p<.05 level. Current results clearly demonstrate a relationship between levels of dependence with severity of withdrawal symptoms experienced, although the precise nature of the association is unclear.

Smokers rate their urges to smoke measured by the QSU as significantly increased following 24-hour abstinence. Both Factor 1 scores (primary intention and appetitive desire to smoke, or positive reinforcement) and Factor 2 scores (avoidance of withdrawal effects and negative affect, or negative reinforcement) were higher in the withdrawn session than the baseline (non-deprived) session. These results are consistent with previous research. Tiffany & Drobes (1991) showed smokers QSU scores on both factors increased incrementally following abstinence periods of 0, 1 and 6 hours. Willner, Hardman & Eaton (1995) showed a similar increase following abstinence periods of between 4 and 14 hours.

The smoker sub-groups were not significantly differentially affected in terms of increase of QSU ratings on either factor. It can be seen however that addicted smokers were rating their urges to smoke higher than non-addicted smokers on both factors. Davies, Willner & Morgan (2000) compared chippers and dependent smokers QSU ratings in response to smoking cues. They found that chippers Factor 1 scores, but not Factor 2 scores, were elevated by cues. This difference was not found in dependent smokers. Exposure to relevant cues and an appropriate period of abstinence are two methods of eliciting craving. If the effects of abstinence on smoking urges can be compared with effects of cue-exposure, Davies et al.'s (2000) findings are analogous

to the current results. Davies et al. (2000) showed that chippers had increased QSU smoking urges relating to positive reinforcement following cue-exposure, and little increase in urges relating to negative reinforcement. They also showed that both types of urges were significantly increased by cue-exposure in regular smokers. The current study broadly supports their findings, and the failure to achieve significance may be due to differences between "chippers" (used by Davies et al. 2000) and "non-addicted smokers" (used in the current research). It was shown that urges of non-addicted smokers pertain to positive rather than negative reinforcement, as these motivations (QSU Factor 1) are the most greatly increased by abstinence and reduced by reinstatement.

Another result in the current study that supports those of Davies et al. (2000) is that higher tobacco dependence (Addiction Index scores) was correlated with greater increases in Factor 2 scores (negative reinforcement) following abstinence. Furthermore, this is concordant with the theory that negative reinforcement is a defining feature of substance dependence (Piasecki et al. 2000), and reduced sensitivity to this aspect may be protecting chippers from developing greater tobacco dependence. However, the existence of causal relationships cannot be automatically inferred from correlation data. Low levels of tobacco dependence or tolerance may explain why negative reinforcement is less important in non-addicted smokers or chippers.

Smokers' total severity of withdrawal symptoms was significantly reduced by 45 minutes of *ad libitum* smoking. These findings are concordant with those of Shiffman

(1989), who compared abstinent smokers before and after a single cigarette and found that reinstatement caused significant reductions in psychological withdrawal symptoms. Addicted and non-addicted smokers did not differ in their symptomatological response to reinstatement, since both groups rated total withdrawal significantly lower after smoking.

This contrasts with Shiffman's (1989) findings that chippers are not significantly subjectively affected by smoking following overnight abstinence. In non-addicted smokers studied in the current research, withdrawal symptoms increase following abstinence and decrease following reinstatement. In chippers, Shiffman (1989) only showed small increases and decreases in symptoms following abstinence then reinstatement; this further exemplifies the difference between chippers and non-addicted smokers discussed previously. The significant effects of reinstatement on withdrawal symptoms would be predicted since non-addicted smokers reported significantly increased withdrawal symptoms following abstinence. In contrast with the response to withdrawal, no individual symptoms differentiated addicted and non-addicted smokers in response to reinstatement, although there was a non-significant trend for addicted smokers to report greater reductions in "craving for tobacco". This finding is broadly consistent with Shiffman (1989), who reported a trend for greater decreases in "desire to smoke" in dependent smokers compared to chippers after one cigarette.

Higher levels of tobacco dependence were correlated with both greater reductions in total withdrawal symptoms and greater reductions in "craving for tobacco" following

reinstatement. These results are interpreted as showing that high-dependence smokers experienced greater increases in withdrawal, craving in particular, following abstinence. *Ergo* they were experiencing greater reductions in symptoms after reinstatement, as their symptoms returned to approximately baseline levels. These results are broadly consistent with theories that levels of dependence will predict severity of withdrawal (Wikler, 1973). High levels of tobacco dependence may reflect more pronounced neuro-adaptation or a greater constitutional need for nicotine (Royal College of Physicians, 2000). Both these phenomena can easily be related to tobacco withdrawal, since more neuro-adaptation or higher nicotine tolerance would mean greater psychopharmacological repercussions during periods of abstinence. This is because homeostatic adaptations caused by chronic nicotine exposure would suddenly be inappropriate for the abstinent state.

Smokers rated their urges to smoke significantly lower following reinstatement than in withdrawal. This occurred in items relating to both positive reinforcement (primary intention and appetitive desire to smoke) and negative reinforcement (avoidance of withdrawal symptoms and negative affect). There was a non-significant trend for *ad libitum* smoking to cause greater reductions in items relating to positive reinforcement in the non-addicted than addicted smokers. This can be explained by the similar levels of urges relating to positive reinforcement reported by both groups during the withdrawn session, whilst the baseline and reinstatement session ratings were lower for the non-addicted group.

Although no comparison data is available showing effects of withdrawal and reinstatement on QSU measures, Shiffman (1989) showed a reduction in "desire to smoke" in both chippers and dependent smokers following reinstatement. Current results showed a non-significant trend for rating changes from withdrawal to reinstatement in urges to smoke relating to negative reinforcement to correlate with levels of tobacco dependence. This correlation was significant when examining the negative reinforcement change from baseline to withdrawn sessions, but did not achieve significance in this comparison perhaps due to greater variation in the ratings on Factor 2 items in the reinstatement session.

Although the functional smoker subgroups used in this study were shown to be valid and discriminatory, it may have been more useful to split the smoker sample into three subgroups rather than two. Chippers (see Chapter 2) could have been examined in their own right whilst moderately addicted smokers could have been studied as a separate subgroup. The small number of addicted smokers may also have contributed to smaller effects and less discriminatory or statistical power in the study. Although 45 minutes of *ad libitum* smoking was likely to have been enough to achieve reinstatement for most subjects, some highly dependent smokers may not have reinstated nicotine levels to baseline through a lack of time, or by smoking fewer cigarettes than they actually desired (i.e. saving cigarettes for another time).

This study demonstrated that 24-hour abstinence from smoking increased ratings of withdrawal in all smokers, and that smokers who were more dependent had greater increases in tobacco craving, restlessness and sleep disturbance. Although all urges to

smoke were increased by withdrawal in all smokers, urges relating to positive reinforcement were most increased in non-addicted smokers, whereas addicted smokers reported greater increases in urges relating to negative reinforcement. All these effects were reversed by reinstatement, with addicted smokers deriving greater relief from tobacco craving than non-addicted smokers. The findings provide insight into particular problems that might be encountered when abstaining from smoking according to levels of tobacco dependence. This may be useful in targeting specific clinical smoking cessation advice for particular types of smokers.

Figure 6.1 Graph showing mean total WSC ratings of the three groups during baseline (non-deprived) and withdrawn sessions

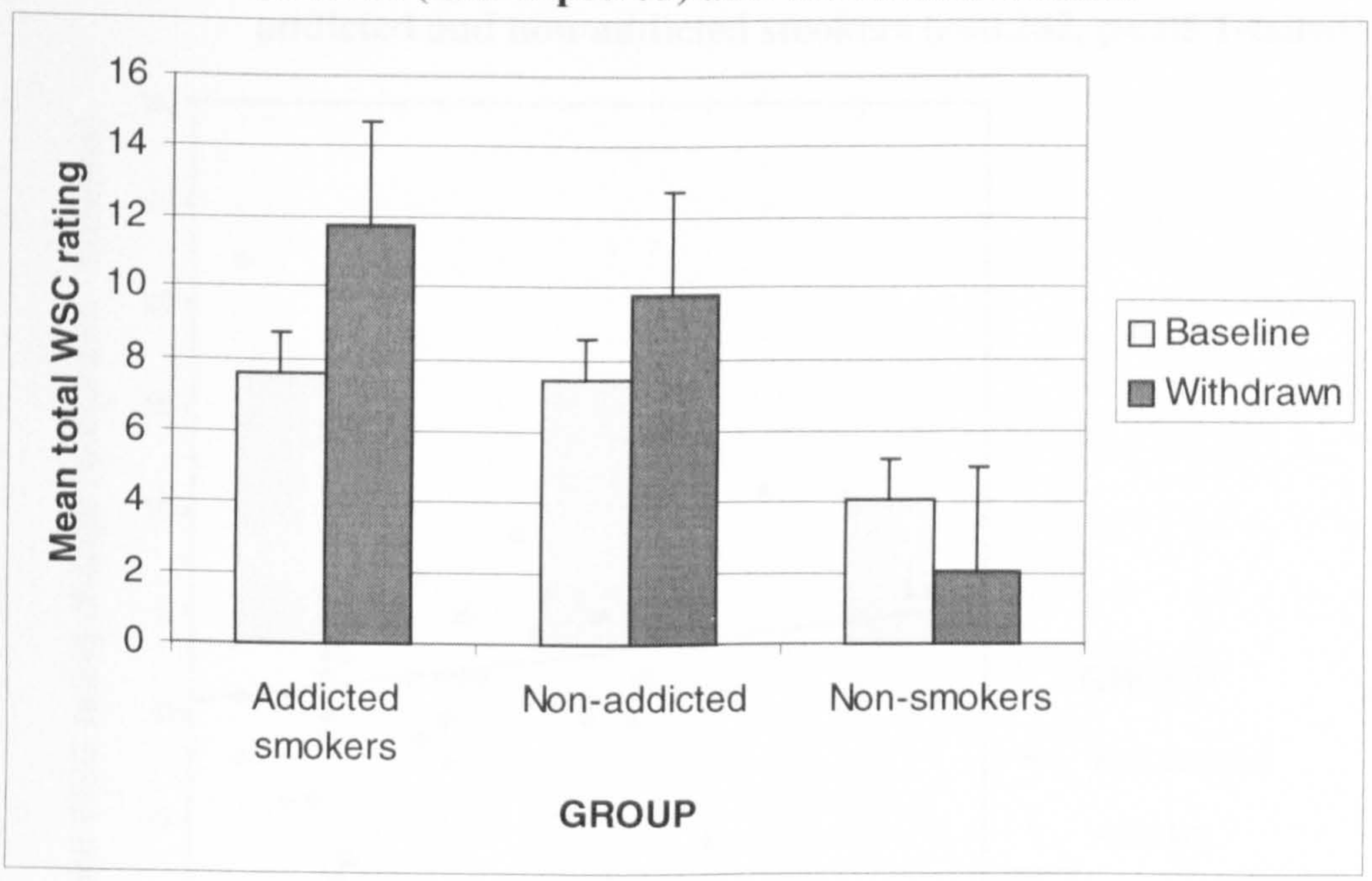


Figure 6.2 Graph showing mean Craving for Tobacco WSC ratings of the three groups during baseline and withdrawn sessions

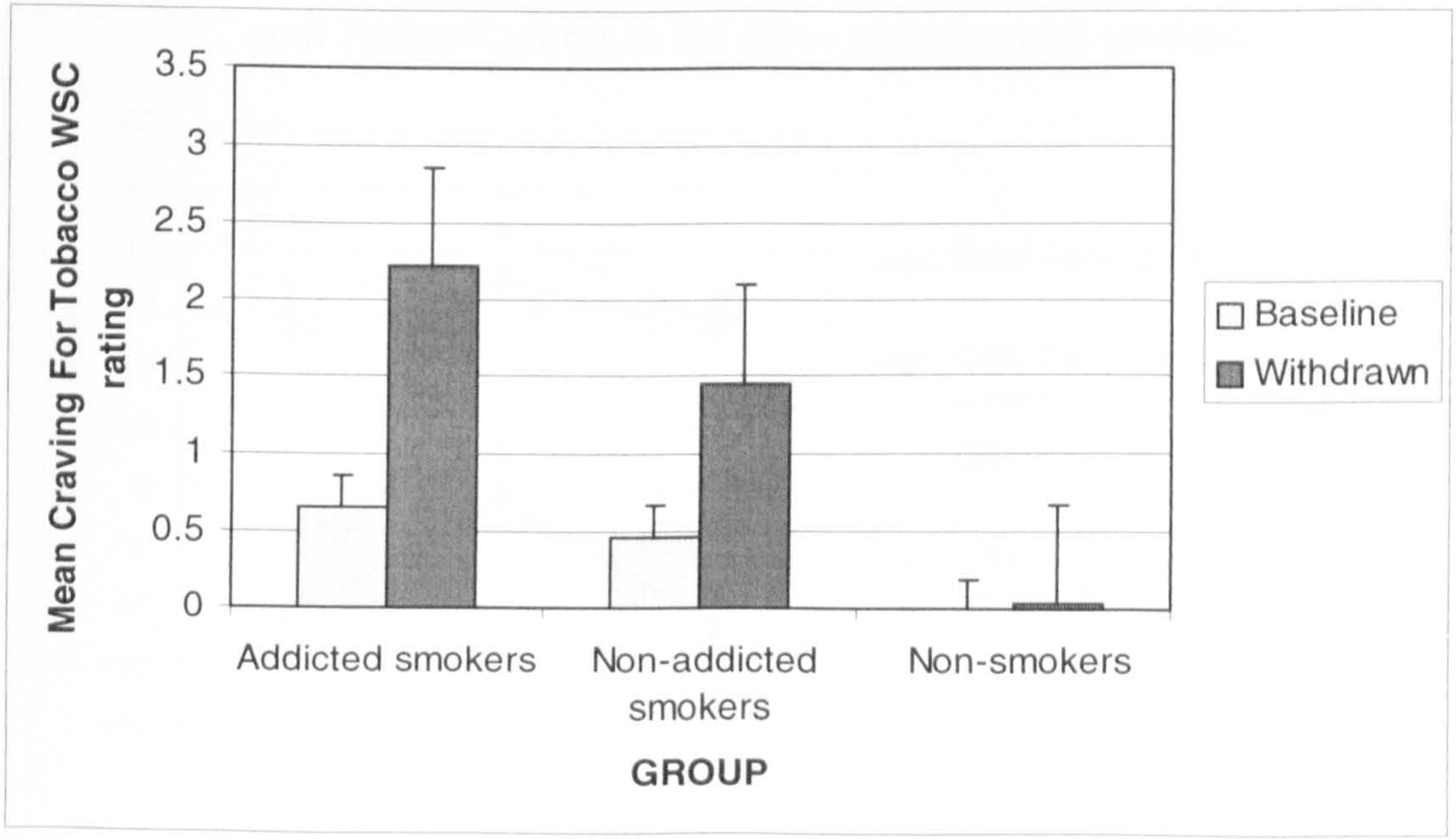


Figure 6.3 **Scatterplot showing relationship between Addiction Index score and change in total WSC ratings (baseline to withdrawn) in addicted and non-addicted smokers (r=0.282, p<.05 1-tailed).**

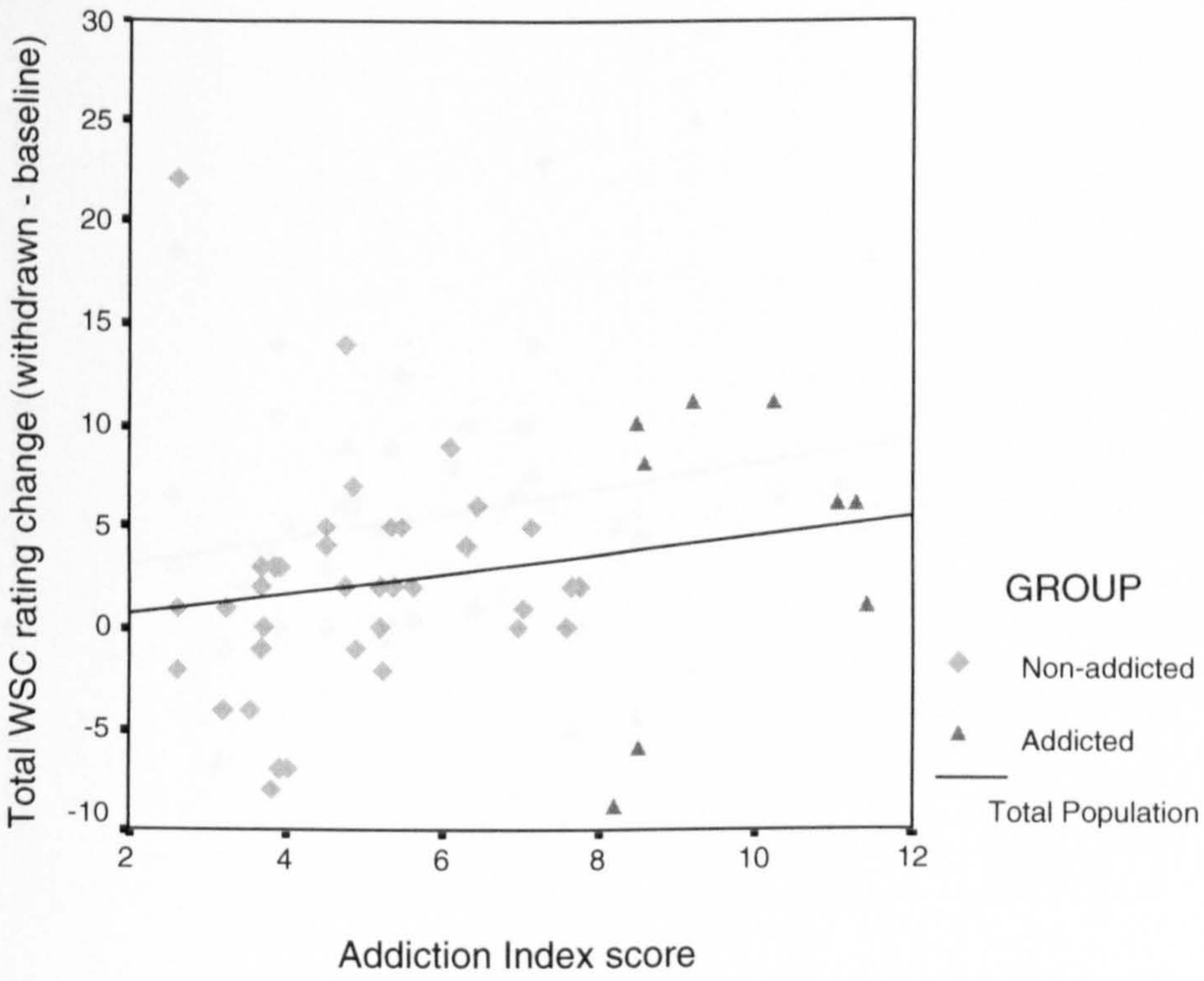


Figure 6.4 **Graph showing addicted and non-addicted smokers QSU Factor 1 and Factor 2 scores in the three experimental sessions.**

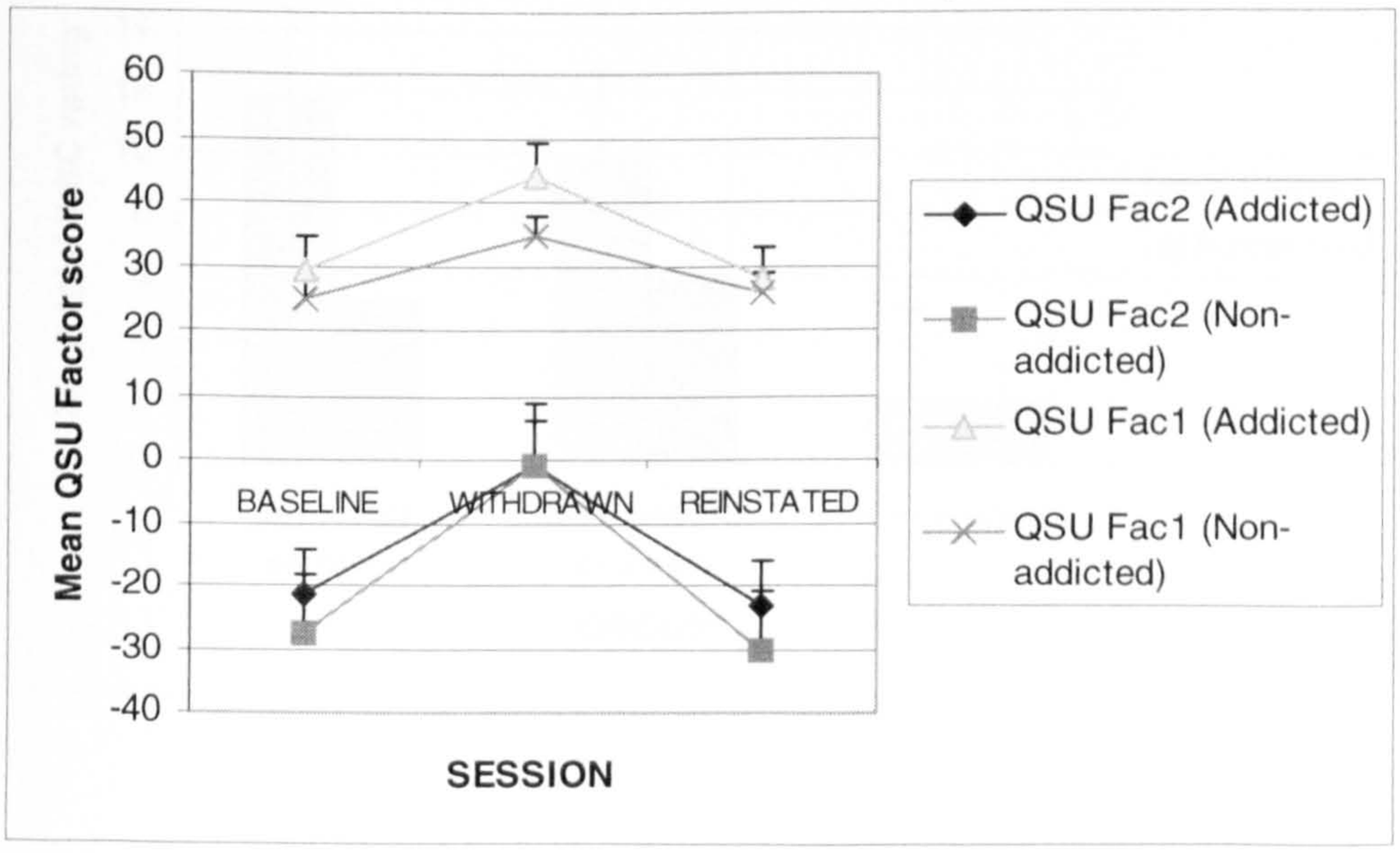


Figure 6.5 **Scatterplot showing relationship between Addiction Index score and change in QSU Factor 2 score (baseline to withdrawn) in addicted and non-addicted smokers (r=0.245, p<.05 1-tailed).**

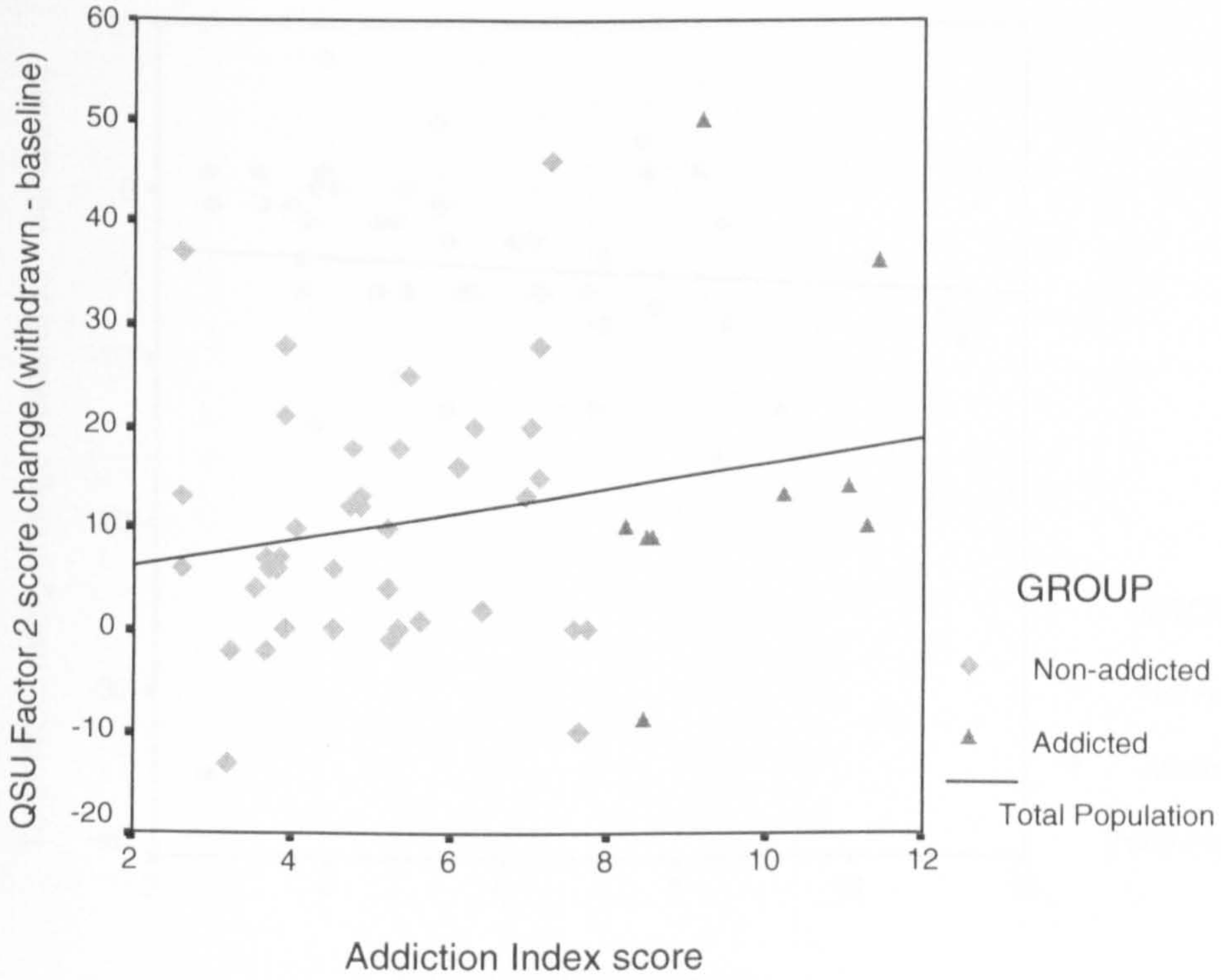


Figure 6.6 **Graph showing mean total WSC ratings of the three subject groups during Withdrawn and Reinstated sessions.**

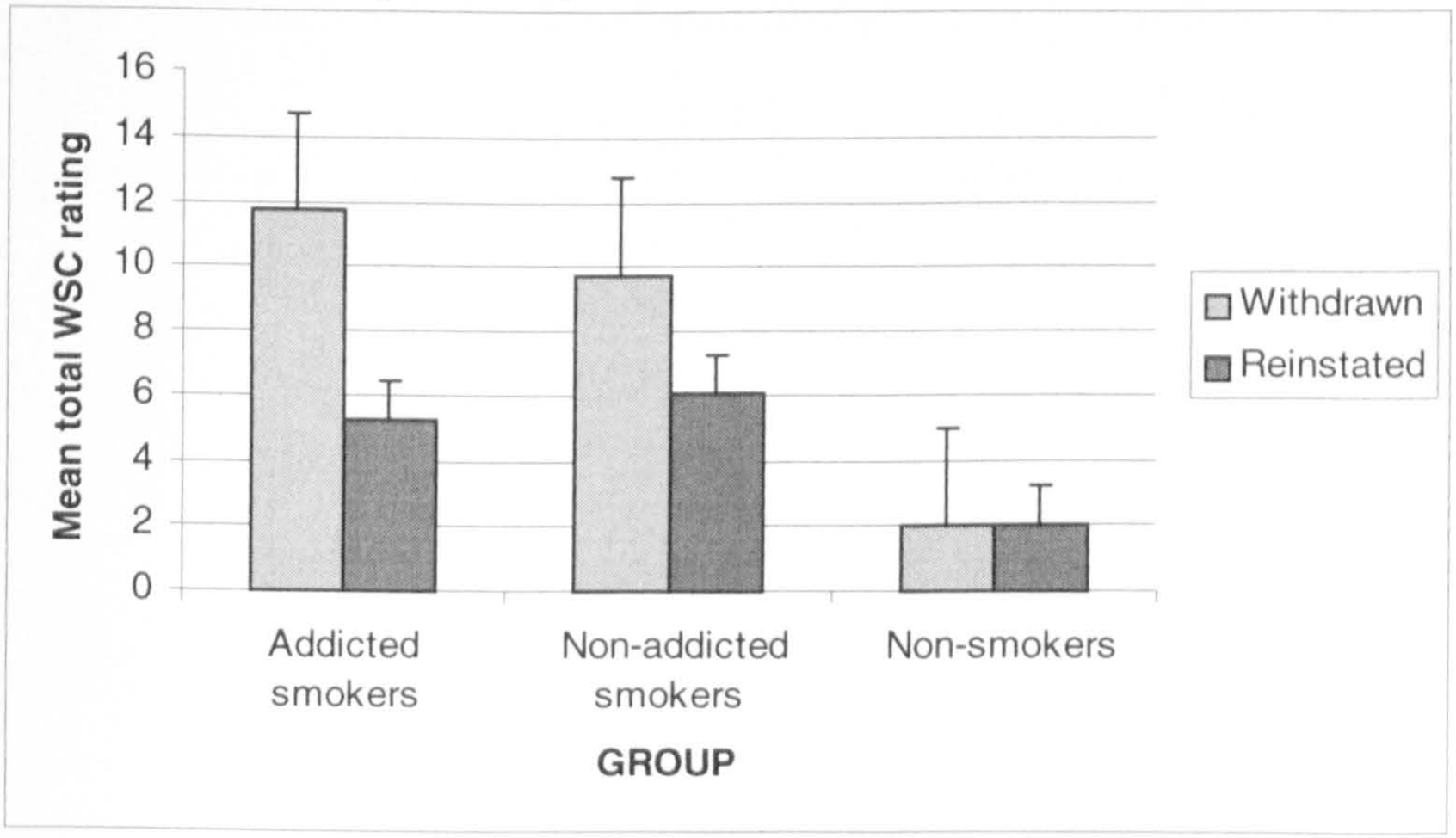


Figure 6.7 **Scatterplot showing relationship between Addiction Index score and change in total WSC ratings (withdrawn to reinstated) in addicted and non-addicted smokers (r=-0.27, p<.05 1-tailed)**

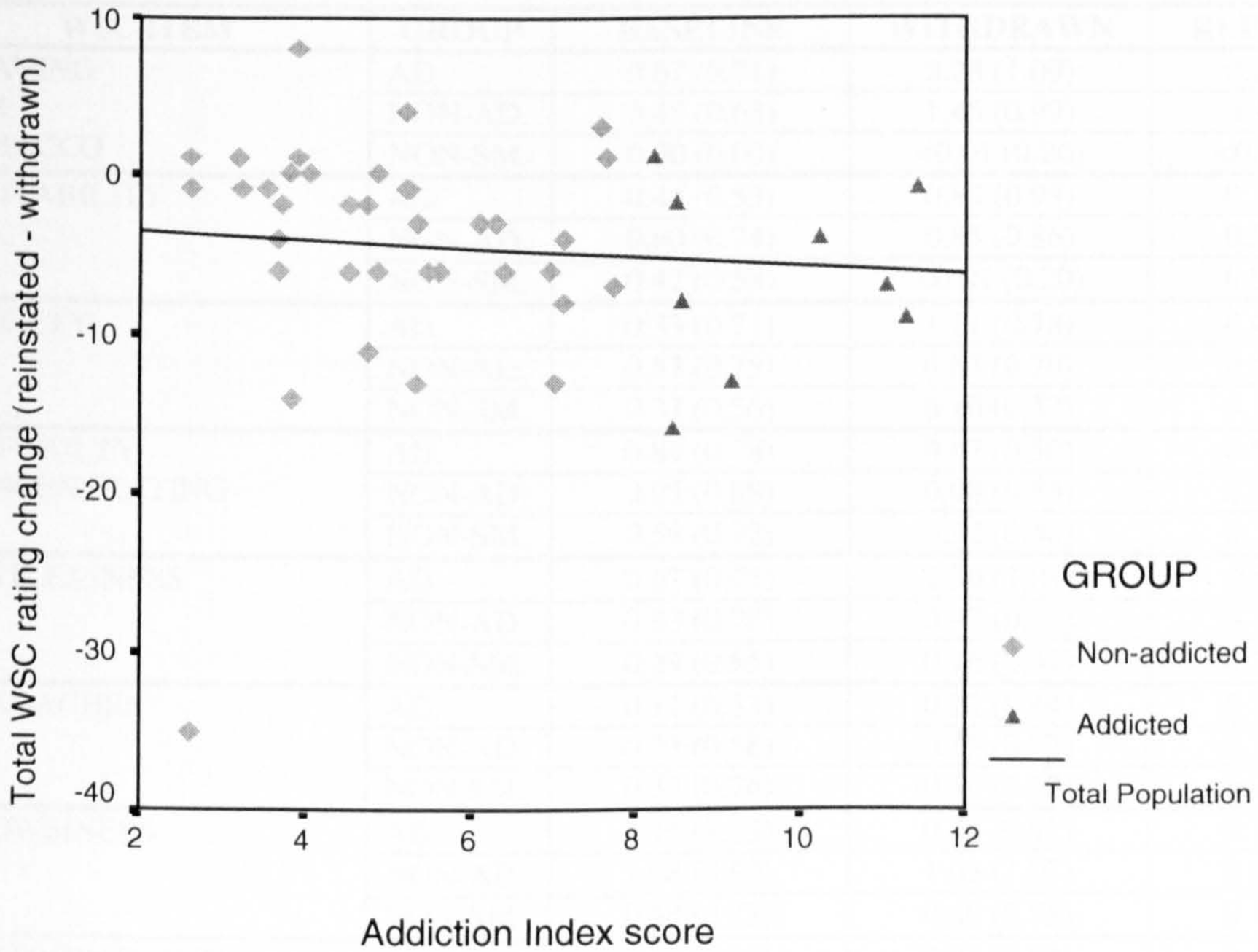


Table 6.1 Mean (standard deviation) withdrawal symptom ratings of addicted smokers, non-addicted smokers and non-smokers in the three test sessions.

WSC ITEM	GROUP	BASELINE	WITHDRAWN	REINSTATED
CRAVING FOR TOBACCO	AD.	0.67 (0.71)	2.23 (1.09)	0.22 (0.44)
	NON-AD.	0.48 (0.68)	1.45 (0.99)	0.40 (0.71)
	NON-SM.	0.00 (0.00)	<0.01 (0.20)	<0.01 (0.20)
IRRITABILITY	AD.	0.44 (0.53)	0.89 (0.93)	0.33 (0.50)
	NON-AD.	0.60 (0.74)	0.85 (0.86)	0.58 (0.75)
	NON-SM.	0.42 (0.58)	<0.01 (0.20)	0.01 (0.28)
ANXIETY .	AD.	0.33 (0.71)	1.11 (0.78)	0.44 (0.73)
	NON-AD.	0.53 (0.75)	0.63 (0.70)	0.40 (0.63)
	NON-SM.	0.33 (0.56)	0.16 (0.37)	0.16 (0.47)
DIFFICULTY CONCENTRATING	AD.	0.89 (0.78)	0.67 (0.50)	0.56 (0.73)
	NON-AD.	0.95 (0.88)	0.98 (0.83)	0.63 (0.67)
	NON-SM.	0.58 (0.72)	0.32 (0.48)	0.24 (0.52)
RESTLESSNESS	AD.	0.67 (0.71)	1.56 (1.01)	0.56 (0.53)
	NON-AD.	0.83 (0.78)	0.97 (0.84)	0.78 (0.83)
	NON-SM.	0.29 (0.55)	0.16 (0.47)	0.20 (0.50)
HEADACHES	AD.	0.11 (0.33)	0.22 (0.44)	0.11 (0.33)
	NON-AD.	0.23 (0.58)	0.35 (0.77)	0.18 (0.50)
	NON-SM.	0.33 (0.76)	0.16 (0.37)	0.01 (0.28)
DROWSINESS	AD.	1.11 (1.05)	0.78 (0.97)	0.78 (0.67)
	NON-AD.	1.08 (0.89)	1.03 (1.07)	0.85 (0.77)
	NON-SM.	0.58 (0.78)	0.40 (0.58)	0.16 (0.37)
GASTROINTESTINAL TRACT DISTURBANCE	AD.	0.11 (0.33)	0.00 (0.00)	0.44 (1.01)
	NON-AD.	0.20 (0.56)	0.28 (0.72)	0.01 (0.35)
	NON-SM.	0.25 (0.61)	0.01 (0.28)	0.00 (0.00)
IMPATIENCE	AD.	0.67 (0.50)	0.78 (0.67)	0.67 (0.71)
	NON-AD.	0.70 (0.72)	0.95 (1.04)	0.78 (0.73)
	NON-SM.	0.33 (0.56)	0.12 (0.33)	0.12 (0.33)
SOMATIC COMPLAINTS	AD.	0.33 (0.71)	0.22 (0.67)	0.11 (0.33)
	NON-AD.	0.15 (0.36)	0.20 (0.56)	<0.01 (0.16)
	NON-SM.	0.01 (0.28)	0.20 (0.58)	0.12 (0.44)
INCREASED EATING	AD.	0.33 (1.00)	0.67 (0.71)	0.00 (0.00)
	NON-AD.	0.35 (0.70)	0.70 (0.79)	0.18 (0.50)
	NON-SM.	0.01 (0.28)	0.00 (0.00)	<0.01 (0.20)
HUNGER	AD.	0.78 (0.97)	0.89 (0.78)	0.67 (0.71)
	NON-AD.	0.60 (0.78)	0.60 (0.84)	0.68 (0.92)
	NON-SM.	0.17 (0.48)	0.00 (0.00)	0.40 (0.65)
UNUSUAL ALCOHOL INTAKE	AD.	0.11 (0.33)	0.33 (0.71)	0.00 (0.00)
	NON-AD.	0.25 (0.71)	0.26 (0.68)	0.10 (0.38)
	NON-SM.	0.13 (0.35)	0.00 (0.00)	0.00 (0.00)
UNUSUAL CAFFEINE INTAKE	AD.	0.44 (0.53)	0.56 (1.13)	0.11 (0.33)
	NON-AD.	0.15 (0.53)	0.30 (0.61)	0.13 (0.46)
	NON-SM.	0.17 (0.64)	0.12 (0.44)	0.12 (0.44)
SLEEP DISTURBANCE	AD.	0.56 (0.53)	0.89 (0.93)	0.22 (0.44)
	NON-AD.	0.38 (0.70)	0.70 (0.97)	0.28 (0.51)
	NON-SM.	0.33 (0.70)	0.24 (0.44)	0.24 (0.52)

Table 6.2 **Mean total WSC ratings for the three groups in the three experimental sessions.**

	MEAN (SD) TOTAL WSC RATINGS		
	BASELINE	WITHDRAWN	REINSTATED
ADDICTED SMOKERS	7.56 (4.33)	11.78 (5.04)	5.22 (3.03)
NON-ADDICTED SMOKERS	7.45 (5.17)	9.79 (6.53)	6.03 (4.67)
NON-SMOKERS	6.36 (4.15)	2.04 (2.59)	2.0 (2.97)

Table 6.3 **Mean "Craving for Tobacco" WSC ratings for the three groups in the three experimental sessions**

	MEAN (SD) "CRAVING FOR TOBACCO" WSC RATINGS		
	BASELINE	WITHDRAWN	REINSTATED
ADDICTED SMOKERS	0.67 (0.71)	2.22 (1.09)	0.22 (0.44)
NON-ADDICTED SMOKERS	0.48 (0.68)	1.45 (0.99)	0.4 (0.71)
NON-SMOKERS	0.0 (0.0)	0.0 (0.2)	0.0 (0.2)

Table 6.4 **Mean QSU Factor 1 scores (positive reinforcement) for the two smoking groups in the three experimental sessions**

	MEAN (SD) QSU FACTOR 1 SCORES		
	BASELINE	WITHDRAWN	REINSTATED
ADDICTED SMOKERS	-21.5 (19.74)	-0.9 (17.15)	-23.1 (22.65)
NON-ADDICTED SMOKERS	-27.53 (14.65)	-0.71 (16.93)	-30.23 (14.15)

Table 6.5 **Mean QSU Factor 2 scores (negative reinforcement) for the two smoking groups in the three experimental sessions**

	MEAN (SD) QSU FACTOR 2 SCORES		
	BASELINE	WITHDRAWN	REINSTATED
ADDICTED SMOKERS	29.4 (11.57)	44.2 (16.57)	27.9 (13.08)
NON-ADDICTED SMOKERS	24.68 (11.26)	34.75 (15.04)	25.7 (11.01)

Chapter 7 – The effects of lofexidine and nicotine on cognitive performance deficits and withdrawal symptoms associated with the tobacco withdrawal syndrome

7.1 Introduction

Nicotine deprivation has been shown to cause impaired cognitive function (Wesnes & Warburton, 1984; Snyder, Davis & Heningfield, 1989; Parrott & Winder 1989), and reinstatement has been shown to reverse these effects, both by smoking (e.g. Houlihan, Pritchard & Robinson, 1996) and by nicotine replacement therapy (e.g. Foulds et al. 1996). These phenomena were investigated in Chapter 3. Symptoms such as difficulty concentrating have been ascribed to the tobacco withdrawal syndrome associated with abstinence in addicted smokers. While the underlying mechanisms of nicotine withdrawal are not well understood, it is believed that lowered mood, anxiety and altered central noradrenergic function are major components of a withdrawal syndrome.

Nicotine is one of several drugs (e.g. alcohol, opiates) that can give rise to a withdrawal syndrome during periods of abstinence. Withdrawal from opiates is associated with hyperactivity of afferent noradrenergic cells in the locus coeruleus (Redmond, Hwang & Gold, 1977) thought to contribute to the anxiety component of the withdrawal syndrome (Weiss, Ciccocioppo, Parsons, Katner, Liu, Zorilla, Valdez, Ben-Shahar, Angeletti & Richter, 2001). α2-adrenoceptor agonists (e.g. clonidine or lofexidine) attenuate this "noradrenergic storm" (Brunning et al. 1986). Although atypical anxiolytics, clonidine and lofexidine have been used successfully to treat the opiate withdrawal syndrome (Gold, Redmond & Kleber, 1978; Strang, Bearn &

Gossop, 1999), blocking signs and symptoms indicating anxiety including apprehension and irritability (Uhde, Redmond & Kleber, 1980).

Anxiety is commonly associated with withdrawal from a variety of addictive substances (e.g. Stewart & Kushner, 2001; Weiss et al. 2001). The locus coeruleus (a brain area rich in α2-adrenoceptors) is implicated in fear and anxiety responses to stimuli, mediated by noradrenaline. Many of the autonomic and psychological manifestations of withdrawal (i.e. sweating, tachycardia, elevated blood pressure) are similar to the exacerbation of anxiety in patients with panic disorder. Uhde et al. (1980) suggest that it is the panic-anxious component of the opioid abstinence syndrome that is most effectively treated by clonidine. Clonidine has also been reported to reduce anxiety in humans and ameliorate anxiety in non-addicted patients (Aghajanian, 1978; Svensson & Strombom, 1977).

α2-receptors can be located both pre- and post-synaptically, with stimulation of each having different effects. Fortuitously, pre- versus post-synaptic mode of action can be determined by the dose of an α2-agonist. At low doses (e.g. 0.2mg clonidine) pre-synaptic autoreceptors such as those in the locus coeruleus are stimulated, attenuating neuronal firing and the release of noradrenaline from terminals (Svensson, Bunney & Aghajanian, 1975; Ong, Ball & Vaughn, 1991). At higher doses post-synaptic actions are triggered, boosting noradrenergic function (Arnsten & Goldman-Rakic, 1985; Arnsten & Cai, 1993). α2-adrenoceptor agonists have sedative side effects (Uhde et al. 1984).

There have been a number of studies examining clonidine and its impact on nicotine withdrawal. Several of these have found that clonidine can indeed mitigate some of the problems associated with tobacco withdrawal. Prochazka et al. (1992) found that clonidine administered transdermally to abstinent smokers reduced some withdrawal symptoms (anxiety and irritability), but did not improve rates of long-term smoking cessation. Ornish et al. (1988) examined the effects of transdermal clonidine on the withdrawal symptoms associated with smoking cessation over six days. They found that craving, anxiety and irritability were reduced by clonidine. Other studies suggest that clonidine does not ameliorate tobacco withdrawal (e.g. McGee & Murray 1989).

There is little research on the effects of α2-agonists on withdrawal-induced cognitive performance deficits, although α2-adrenoceptors are also known to play a role in cognitive performance. The locus coeruleus noradrenergic system is associated with consolidation and learning (Crow, 1968; Kety, 1970), selective attention (Mason & Iversen, 1979) and prefrontal cognitive processing (e.g. Arnsten & Goldman-Rakic, 1985; Sahakian, Coull & Hodges, 1994). Low doses of clonidine have been demonstrated to selectively impair cognitive performance in humans and animals (Arnsten & Goldman-Rakic, 1985; Frith, Dowdy, Ferrier & Crow, 1985). The findings are consistent with the theory that noradrenaline is involved in preventing people from becoming distracted by irrelevant stimuli.

Low doses of clonidine have also been shown to impair performance on a focused attention task (Smith & Nutt, 1996) and a rapid visual information processing task (Coull et al. 1995). This is contrasted with findings that idazoxan (an α2-antagonist) improved performance on a categoric search task (Smith et al. 1992a). Clark, Geffen

& Geffen (1989) however reported that clonidine reduced errors on the Posner covert orientation of attention task (Posner, 1980). These studies therefore suggest that α2-agonists broaden the focus of attention, whereas enhanced noradrenergic function (as induced by α2-antagonists or opiate withdrawal) narrows the focus of attention.

There may be common ground among withdrawal syndromes associated with many drugs of dependence in terms of psychopharmacology and behavioural effects. The importance of anxiety both as a baseline discriminator and as a differentially prominent withdrawal symptom justifies looking further at the effects of this class of drug on the tobacco withdrawal syndrome. Although clonidine effects on tobacco withdrawal have been investigated, lofexidine has fewer side effects and promotes less hypotension (Gerra et al. 2001), and therefore may ultimately have more clinical significance. Examination of the impact of lofexidine on tobacco withdrawal may also improve our understanding of this withdrawal syndrome as well as offer increased pharmacotherapeutic options in terms of treating nicotine dependence. If lofexidine can ameliorate nicotine withdrawal in a similar way to opiate withdrawal, it is important to establish whether different symptoms are differentially affected.

Cognitive tasks demonstrating sensitivity to effects of tobacco withdrawal and reinstatement in Chapter 3 were chosen for use in this study. These were a focused attention task, categoric search task, and rapid visual information processing task.

In order to clearly present all the findings of this study, the current chapter splits following the Method section to present the mood and cognitive performance results and discussion (7A), followed by the withdrawal questionnaire symptomatology

results and discussion (7B). These will be summarised with a general discussion at the close of the chapter.

Hypotheses (7A):

I. that 24-hour nicotine withdrawal will result in performance decrements on cognitive tasks, including reduced accuracy and increased reaction times on trials of the focused attention and categoric search tasks, and fewer hits on the repeated digits vigilance/RVIP task).

II. that 24-hour nicotine withdrawal will affect visual analogue scale ratings of mood, reducing alertness and hedonic tone, and increasing anxiety.

III. that NRT (Nicorette© inhalator) will reverse these withdrawal-induced mood and performance decrements more effectively than placebo.

IV. that lofexidine will reverse withdrawal-induced mood and performance decrements where impaired attention or increased anxiety is fundamental, better than placebo and as effectively as NRT.

Hypotheses (7B):

V. that 24-hour nicotine withdrawal will increase subjects' self-report ratings of withdrawal symptoms.

VI. that 24-hour nicotine withdrawal will increase subjects' ratings of urges to smoke (particularly on Factor 2 scores on QSU).

VII. that 24-hour nicotine withdrawal will negatively affect acute mood states measured by POMS.

VIII. that NRT (Nicorette© inhalator) will reverse these nicotine withdrawal symptoms, urges to smoke and negative mood states more effectively than placebo.

IX. that lofexidine will reverse nicotine withdrawal symptoms, urges to smoke and negative mood states better than placebo and as effectively as NRT.

7.2 Method

7.2.1 Design

This study was a double-blind placebo-controlled pseudo-randomised repeated measures design with the following conditions: lofexidine capsule, placebo capsule, nicotine inhalator and placebo inhalator. Performance measures used were Broadbent et al.'s (1989) focused attention and categoric search tasks (measuring accuracy and reaction time variables), and repeated digits vigilance / rapid visual information processing (RVIP) task (measuring hits, false alarms and reaction times). Pre- and post-test mood measures were also taken using visual analogue scales (measuring alertness, hedonic tone and anxiety). See Appendices V, VII, VIII and X for full descriptions of the variables. Questionnaires administered were Withdrawal

Symptoms Checklist, Other Withdrawal Symptoms checklist, Questionnaire of Smoking Urges and Profile of Mood States. These are described in Section 7.2.3.

Participants attended two experimental weeks that were normally consecutive. One was a 'nicotine week' consisting of a Baseline Session (Monday), Placebo Session (Tuesday or Friday) and Drug Session (Friday or Tuesday). Another was a 'lofexidine week' also consisting of a Baseline Session (Monday), Placebo Session (Tuesday or Friday) and Drug Session (Friday or Tuesday). All subjects performed all sessions: those who received placebo on Tuesday received drug on Friday, and vice versa. This was counterbalanced to control for order effects, as was order of nicotine/lofexidine week.

The United Bristol Healthcare Trust granted ethical approval for this study.

7.2.2 Subjects

Twelve addicted smokers (6 male, 6 female) were recruited from student sources via posters around the University campus and mail-shots on various e-mail lists. Ages ranged from 19-45, mean=24.4 (SD 7.7). Smokers' addiction status was assessed using the Fagerstrom Tolerance Questionnaire (FTQ) described in Chapter 2. Smokers scoring 4 or higher on the FTQ and smoking 15 or more cigarettes per day were considered addicted and accepted on the study. These participants later completed the SQB (see Chapter 2), and all were found to have an Addiction Index score higher than 8.0 (mean=10.4, SD 1.12), and could therefore be classed as addicted smokers using the same criteria previously utilised in the thesis.

7.2.3 Questionnaires

A pre-test questionnaire (PTQ) booklet was compiled and used in a similar way to that described in Chapter 6. This pre-test questionnaire (PTQ) features a short questionnaire asking for details of food, alcohol and tobacco consumption over the previous 24 hours (see Appendix XVI); it also includes The Profile of Mood States (POMS), WSC and QSU (see Chapter 6) and Other Withdrawal Symptoms (OWS). Questionnaire data will be described in section 7B.

Withdrawal Symptoms Checklist (WSC)

This is a fifteen-item checklist based on the Hughes & Hatsukami (1986) study on tobacco withdrawal. It features eight items taken from the DSM-III symptom list for the tobacco withdrawal syndrome, plus further items added by the authors. It presents each item (craving for tobacco, irritability, etc.) with 4 check-boxes labelled 0 to 3. 0=not present, 1=mild, 2=moderate, 3=severe. See Appendix XIV.

Other Withdrawal Symptoms (OWS)

This is a twenty-item checklist based on the withdrawal symptoms reported in opiate withdrawal likely to be associated with noradrenaline (Strang, Bearn & Gossop, 1999). Each item is presented with a 10-point Likert-type scale with ratings from 0 (not present) through to 9 (severe). See Appendix XVII.

Questionnaire of Smoking Urges (QSU)

This is a 32-item questionnaire developed and validated by Tiffany & Drobes (1991). Subjects are presented with positive or negative statements regarding urge to smoke. Subjects were asked to indicate on a Likert-type scale how strongly they agree or

disagreed with each statement. Each item was scored on a scale of 1 (strongly disagree) to 7 (strongly agree). See Appendix XV.

Profile of Mood States

The mono-polar POMS questionnaire (McNair et al. 1971; 1981) was utilised to examine acute mood states. This was used in conjunction with the pre- and post-test mood scales included in the computer task battery. The POMS is a 65-item questionnaire asking subjects to rate a mood state (e.g. sad, angry, lively) on a 5-point Likert-type scale (0=Not at all, through to 4=Extremely). See Appendix XVIII.

7.2.4 Materials

Lofexidine was administered as a 0.2mg tablet, which has been previously used safely. Tablets were placed inside lactulose capsules, randomised by a third party and placed in labelled grip-bags. Placebo in this trial was a comparable lactulose capsule.

Nicotine was administered via a Nicorette© inhalator device. This is a plastic tube-shaped mouthpiece containing a Nicorette© cartridge containing 10mg nicotine and menthol flavouring. Subjects were instructed to use these in a particular way; i.e. by taking eight "puffs" on the inhalator. Subjects were asked to inhale deeply through the inhalator, and warned that there is far more resistance than with normal cigarettes. The placebo version of these devices was the same except the cartridge was altered: the polythene pellet within was removed and replaced with a Swan slimline filter tip bent double. Both placebo and drug cartridges were treated with a drop of Olbas oil tincture overnight prior to use. This was to mask taste and aroma differences between nicotine and placebo.

At appropriate times, subjects were breathalysed in order to check whether they had successfully abstained from smoking for the previous 24 hours. This was done using a MicroMedical MicroCO carbon monoxide breathalyser. A count of less than 10 parts per million was accepted as proof that the subject had abstained and could continue with the trial.

7.7.5 Computer tasks

The tasks were chosen from those described in Chapter 3 showing marked impact of nicotine withdrawal, and were administered using Amstrad PCs running DOS.

Mood - Visual analogue mood scales

Subjective mood is assessed using 18 computerised visual analogue mood scales. These 18 scales were presented successively. Ultimately these are factor scored and yield scores for three measures: *anxiety, hedonic tone and alertness.* See Appendix V for a full description.

Performance tests

Focused attention task

Participants were presented with ten practice trials followed by 'n' blocks of 64 trials. In each block there were equal numbers of 'near' or 'far' conditions, 'A' or 'B' responses and equal numbers of the four distracter conditions. The nature of the previous trial was also controlled. See Appendix VII for a full description of this task.

Categoric search task

The number of 'near' and 'far' stimuli, 'A' and 'B' responses, and distracter and blank conditions were controlled. Half of the trials lead to compatible responses (i.e., the letter A on the left side of the screen, or letter B on the right). The nature of the preceding trial was also controlled. In other respects (practice, number of trials, etc.) the task is identical to the focused attention task. See Appendix VIII for a full description of this task.

Repeated digits detection (RVIP/vigilance) task

This visual cognitive vigilance task measures the ability to detect targets at irregular intervals. In this task lasting 5 minutes, participants were shown successive presentations of three digit numbers in the centre of the screen at the rate of 100 per minute. Each three-digit number usually differed from the one immediately preceding it, with one out of the three digits being replaced with a different digit (e.g. 463, 563, 562). Eight times per minute the same three-digit number will be presented on successive trials. Participants were required to detect and respond to these repetitions as quickly as possible by pressing a key. See Appendix X.

7.2.6 Procedure

The experimental week procedure can be observed as a timetable in Table 7.1.

Familiarisation

This session was performed at any time prior to the commencement of the first week of the study. On arrival at the Psychology Research Unit, participants were issued with standardised verbal instructions.

Subjects were asked to read the information sheet (see Appendix XIX) and gave written consent regarding participation (see Appendix XX). Once complete they were asked to perform a shortened 15-minute version of the computer test battery. When finished, subjects completed a Smoking Questionnaire Battery (see Chapter 2).

Baseline

This session tested participants under normal, non-abstinent conditions. Each subject performed this session at the start of each experimental week (nicotine and lofexidine). It commenced Monday at 9.00 a.m., with subjects asked to smoke normally prior to arrival.

9.00 a.m. Pre-Test Questionnaire booklets (see Appendix XVI) completed.

9.10a.m. Computer test battery performed.

Experimental session

Both experimental weeks featured drug and placebo condition experimental sessions, which were randomly allocated to Tuesday and Friday. These conditions were single-blind in the nicotine week and double-blind in lofexidine week.

9.00 a.m. Pre-Test Questionnaire booklets (see Appendix XVI) completed.

9.05 a.m. Subjects breathalysed using the MicroCO.

9.10 a.m. Computer test battery performed.

9.30 a.m. Subjects remain in booths for 1 hour break (resting).

9.32 a.m. (Lofexidine week) – Subjects administered lofexidine or lactulose capsule and 200ml water and instructed to swallow the capsule immediately.

10.10 a.m. (Nicotine week) – Subjects administered nicotine or placebo inhalator. Subjects were instructed to familiarise themselves with the airflow resistance of the device then to take 8 'puffs' on the device; 'puff' being defined as breathing in through the inhalator straight into their lungs for as long as was comfortable. Subjects told to take normal breaths between 'puffs'.

10.20 a.m. (Lofexidine week) – Subjects' blood pressure taken.

10.30 a.m. Pre-Test Questionnaire booklets (see Appendix XVI) completed.

10.35 a.m. Computer test battery repeated.

11.00 a.m. (Friday, second week) – Subjects completed documentation and informed when they would receive their remuneration, then thanked and debriefed.

SECTION 7A

7A.1. Statistical analyses

Analysing the lofexidine and nicotine study weeks as two separate 2x2 (drug versus placebo, pre-treatment versus post-treatment) factorial repeated measures analyses of variance was considered. Although this method had increased power relative to the analysis method ultimately used and removed the need for conservative Bonferroni corrections, there were several good reasons why the 2x2 model was rejected in this instance. To merely investigate the nicotine or lofexidine effects, using the 2x2 model might have been preferable, however we were also interested in withdrawal effects; i.e. a direct comparison between baseline and pre-treatment session means. We were also interested in explicit placebo effects. These extra comparisons fall outside the

standard remit of the 2x2 factorial design. Furthermore, the validity of baseline data as covariates in the 2x2 model is questionable. Since both the pre-treatment (withdrawn) and post-treatment (inhalator/capsule) states were very different to normal non-deprived baseline conditions, the inclusion of the latter in the model may lack statistical and theoretical relevance.

Analysis using the 2x2 factorial method was carried out in order to contrast with the single-factor model finally chosen. Many of the results observed were highly comparable between the two methods. For example, the lofexidine effect of increasing time taken to encode new information in the Focused Attention task (section 7A.2.1.1.2.2) showed similar findings using the 2x2 ANOVA ($F\{1,10\}=14.7$, $p<.005$). Other effects, however, were not corroborated by the alternative analysis, probably due to the direct involvement of placebo effects in the model. For example the nicotine effect of reducing the Eriksen effect in the Focused Attention task (section 7A.2.1.1.2.2) was not found using the 2x2 ANOVA ($F\{1,10\}=2.3$, $p=0.16$). To minimise the likelihood of Type II errors, and for the reasons outlined in the previous paragraph, the 2x2 factorial analysis was not utilised in the global analyses of data in this chapter. The same rationale was also applied to analyses in Section 7B.

Repeated measures analysis of variance was carried out on the performance data using SPSS 9.0 statistical package. All 10 sessions were compared with each other as 10 levels of the same variable: Time. Using this model allowed us to explicitly investigate the effects of withdrawal by comparing baseline with pre-treatment (abstinent) sessions, and placebo effects by comparing pre-placebo and post-placebo sessions. Due to the large number of comparisons, session means contrasts were

examined using Bonferroni correction for multiple comparisons. Mood data was factorised to give scores on three axes (alertness, hedonic tone and anxiety). Order effects were not formally examined due to the randomised cross-over structure of the design.

Further correction for multiple comparisons in the Focused Attention and Categoric Search tasks, since both tests examined large numbers of variables, was considered but not performed as it was deemed inappropriate. Although many statistical tests were performed in the analyses of both tasks, the precise variables tended to be highly correlated components of either accuracy or reaction time on the global cognitive attributes measured. Correcting for multiple comparisons would have therefore increased the likelihood of Type II error.

7A.2. Results

7A.2.1. Cognitive Performance

An overview of the effects of withdrawal, and subsequent effects of lofexidine, nicotine and placebo on accuracy and reaction time on the three cognitive performance tasks can be observed in Table 7.2.

7A.2.1.1. Focused Attention Task

This task measures 46 different variables: of these, 12 showed a significant effect of session: 10 of these were discrete accuracy variables and two were derived reaction time-based variables.

7A.2.1.1.1. Accuracy (F.A.T.)

7A.2.1.1.1.1. Withdrawal effect: comparison of baseline (non-deprived) session with pre-drug/pre-placebo

Subjects' accuracy on several variables in the focused attention task was impaired in withdrawn sessions.

Repeated measures analysis of variance indicated reduced accuracy in responding to targets presented alone or with an asterisk ($F\{9,99\}=3.11$, $p<.002$), with pre-drug nicotine sessions less accurate than nicotine baseline ($p<.05$) and pre-placebo lofexidine sessions less accurate than lofexidine baseline ($p<.05$) (see Table 7.3, Figure 7.1). Reduced accuracy can be seen in all sessions compared to baseline. These effects did not survive Bonferroni correction for multiple comparisons.

The Eriksen effect (spatial interference) on accuracy of responses was affected by session as revealed by ANOVA ($F\{9,99\}=2.24$, $p<.05$). Subjects were less prone to spatial interference effects on accuracy when abstinent, as significant differences were found between nicotine week baseline and the pre-drug session ($p<.025$). These effects did not survive Bonferroni correction for multiple comparisons. No significant withdrawal effects are demonstrated in the lofexidine week.

Accuracy was also affected by session when the target was presented with *disagreeing* stimuli (e.g. if 'A' was the target, the distracters were 'B') in the 'near' position ($F\{9,99\}=2.94$, $p<.01$). Both pre-placebo ($p<.05$) and post-placebo ($p<.01$) sessions showed greater impact of near disagreeing distracters than in lofexidine

baseline, as accuracy in the latter sessions was lower. These effects did not survive Bonferroni correction for multiple comparisons.

Accuracy of response when a target was *repeated* from previous trial (e.g. 'A' followed by 'A') was also shown to be significantly affected by session ($F\{9,99\}=3.77$, $p<.001$). Greater accuracy was observed in the lofexidine baseline session than a withdrawn (pre-placebo) session ($p<.025$). This effect did not survive Bonferroni correction. Furthermore, accuracy of response when a target was *alternated* from previous trial (e.g. 'B' when previous trial was 'A') also demonstrated a significant session effect ($F\{9,99\}=2.84$, $p<.01$). Mean accuracy is significantly lower in the pre-placebo ($p<.05$) lofexidine session compared to lofexidine baseline (see Figure 7.2 and Table 7.4). This effect survived Bonferroni correction for multiple comparisons.

Response accuracy was significantly affected by session when asterisks were presented in the 'near' position with the target ($F\{9,99\}=2.41$, $p<.025$). Accuracy was shown to be lower in the pre-drug session ($p<.025$) compared to baseline in the nicotine week. These effects did not survive Bonferroni correction for multiple comparisons.

Presenting disagreeing stimuli in the 'near' location to the target has an effect of decreasing accuracy. This effect differed between sessions as shown by repeated measures ANOVA ($F\{9,99\}=2.52$, $p<.025$). The impairing effect of 'near'-placed distracters was significantly greater in the baseline session than the pre-drug session ($p<.025$). This effect did not survive Bonferroni correction for multiple comparisons.

7A.2.1.1.1.2. Lofexidine effect

Variables pertaining to accuracy on the focused attention task were shown to be not sensitive to effects of lofexidine in 24-hour tobacco withdrawn subjects. This was investigated using repeated measures analysis of variance to examine main effects of 'session', and Bonferroni corrected multiple comparisons of estimated marginal means. No post-lofexidine sessions differed significantly from the pre-lofexidine sessions.

7A.2.1.1.1.3. Nicotine effect

Variables pertaining to accuracy on the focused attention task were shown to be not sensitive to effects of nicotine in 24-hour tobacco withdrawn subjects. This was investigated using repeated measures analysis of variance to examine main effects of 'session', and Bonferroni corrected multiple comparisons of estimated marginal means. No post-nicotine sessions differed significantly from the pre-nicotine sessions.

7A.2.1.1.2. Reaction time (F.A.T.)

7A.2.1.1.2.1. Withdrawal effect: comparison of baseline with pre-drug/ pre-placebo

Variables pertaining to reaction times on the focused attention task were shown to be not sensitive to 24-hour abstinence from tobacco using repeated measures analysis of variance to investigate main effects of 'session', and Bonferroni corrected multiple comparisons of estimated marginal means. No withdrawn sessions differed significantly from the respective baseline sessions.

7A.2.1.1.2.2. Lofexidine effect

Subjects' reaction times on the focused attention task were impaired by lofexidine. Analysis of variance showed that mean time taken to encode a new response (Σ time responding to targets alternating from previous trial minus Σ time responding to targets repeating from previous trial) was affected by session ($F\{9,99\}=1.97$, $p<.05$). Scores on this variable shows that lofexidine increases the amount of time taken to encode a new response on the focused attention task (post-lofexidine session differs to pre-lofexidine session ($p<.005$)). See Figure 7.3 and Table 7.5. This effect did not survive Bonferroni correction for multiple comparisons.

7A.2.1.1.2.3. Nicotine effect

ANOVA showed a main effect of session on spatial interference (Eriksen effect) ($F\{9,99\}=2.29$, $p<.025$). The Eriksen effect was reduced by the administration of nicotine. Pre-nicotine and post-nicotine session means differed significantly ($p<.025$), although this effect did not survive Bonferroni correction for multiple comparisons.

7A.2.1.2. Categoric Search Task

This task examined 44 variables on the Broadbent (1989) categoric search task. Fourteen of these variables showed a significant effect of session when examined using repeated measures analysis of variance, including 4 variables regarding accuracy and 10 reaction time variables.

7A.2.1.2.1. Accuracy (C.S.T.)

7A.2.1.2.1.1. Withdrawal effect: comparison of baseline with pre-drug/ pre-placebo

Subjects' accuracy on several variables in the categoric search task was impaired in withdrawn sessions.

Analysis of variance (repeated measures) showed a main effect of session on mean accuracy responding to targets presented in the *same* location as the previous trial ($F\{9,99\}=2.00$, $p<.05$). Lofexidine week baseline was more accurate than both the pre-placebo and pre-drug sessions during that week (both $p<.05$). These differences did not survive Bonferroni correction for multiple comparisons.

Mean accuracy on trials where targets are in blank (no distracter), 'far' position, incompatible (e.g. target presentation on left, correct response key on right) conditions were shown by ANOVA to be subject to a main effect of session ($F\{9,99\}=1.99$, $p<.05$). Accuracy is significantly higher in the baseline sessions than in the withdrawn sessions, shown by differences between baseline and pre-drug session in the nicotine week ($p<.025$). Similar differences were also shown between baseline and both pre-drug ($p<.01$) and pre-placebo ($p<.05$) sessions in the lofexidine week. These effects did not survive Bonferroni correction for multiple comparisons.

7A.2.1.2.1.2. Lofexidine effect

Lofexidine improves accuracy on the categoric search task. Effects were observed in mean accuracy responding to targets in blank (no distracter), 'far' and 'incompatible' conditions ($F\{9,99\}=1.99$, $p<.05$). Subjects' responses to these trials were more

accurate after the administration of lofexidine, as pre-lofexidine means are lower than post-lofexidine ($p<.05$). This effect did not survive Bonferroni correction for multiple comparisons.

7A.2.1.2.1.3. Nicotine effect

As with the focused attention task, variables pertaining to accuracy on the categoric search task were shown to be not sensitive to effects of nicotine in 24-hour tobacco withdrawn subjects. This was investigated using repeated measures analysis of variance to examine main effects of 'session', and Bonferroni corrected multiple comparisons of estimated marginal means. No post-nicotine sessions differed significantly from the pre-nicotine sessions.

7A.2.1.2.2. Reaction time (C.S.T.)

7A.2.1.2.2.1. Withdrawal effect: comparison of baseline with pre-drug/ pre-placebo

Subjects' reaction times on several variables in the categoric search task were improved in withdrawn sessions.

Mean reaction time responding to trials where targets were presented in the same location as the previous trial was significantly different according to session ($F\{9,99\}=3.23$, $p<.01$). Response times were significantly slower in baseline than pre-placebo session ($p<.05$) in the lofexidine week. This effect did not survive Bonferroni correction for multiple comparisons.

Analysis of variance revealed a main effect of session on mean reaction time to trials when the target is repeated from the previous trial (e.g. target was 'A' in both current and previous trial) ($F\{9,99\}=3.27$, $p<.01$). Baseline reaction times on these trials are significantly slower than pre-placebo session ($p<.025$) in the lofexidine week (Figure 7.4 and Table 7.6). These effects did not survive Bonferroni correction for multiple comparisons.

Mean reaction time in trials where the target was presented *with* a distracter in the 'far' and 'incompatible' position was shown to be significantly affected by session ($F\{9,99\}=3.79$, $p<.001$). In the lofexidine week response times were significantly slower in baseline sessions than in pre-placebo session ($p<.05$). Mean reaction times on trials where a distracter was present in the 'near' and 'incompatible' conditions was also significantly affected by session ($F\{9,99\}=2.10$, $p<.05$). Response times were slower in baseline sessions than in withdrawal; with significant differences observed between baseline and pre-placebo sessions ($p<.05$) in the lofexidine week. These effects did not survive Bonferroni correction for multiple comparisons.

7A.2.1.2.2.2. Lofexidine effect

Lofexidine improved reaction time performance on several variables of the categoric search task. Analysis of variance showed an effect of lofexidine on the changes caused to mean reaction time by presenting targets with irrelevant stimuli (digits), in the 'far' and 'compatible' condition ($F\{9,99\}=2.27$, $p<.025$). Comparisons showed the slowing effect on response times caused by irrelevant stimuli was significantly less in the post-lofexidine session compared with the pre-lofexidine session ($p<.05$), although this effect did not survive Bonferroni correction (Figure 7.5 and Table 7.7).

Lofexidine effects were also observed on mean reaction time to trials where the target is presented with a distracter, in the 'far' and 'incompatible' position ($F\{9,99\}=3.79$, $p<.001$). Subjects' response times are significantly faster in this condition after the administration of lofexidine, as pre-lofexidine and post-lofexidine sessions differed ($p<.05$). This effect did not survive Bonferroni correction for multiple comparisons.

Placebo effects (significant differences between pre-placebo and post-placebo sessions) were found on the mean reaction time when the target category is repeated from previous to current trial (i.e. 'A' followed by 'A') ($F\{9,99\}=3.27$, $p<.01$). Reaction times in this condition were faster following placebo capsule (pre-placebo versus post-placebo, $p<.05$). This effect did not survive Bonferroni correction.

7A.2.1.2.2.3. Nicotine effect

Nicotine improved subjects' reaction times on certain variables in the categoric search task. ANOVA showed nicotine effects on mean reaction time to targets presented in the same location as the previous trial ($F\{9,99\}=3.23$, $p<.01$). Subjects' response times are significantly faster in the post-nicotine session compared to the pre-nicotine session ($p<.05$) (Figure 7.6 and Table 7.8), although this effect did not survive Bonferroni correction.

Nicotine effects were also demonstrated on mean reaction time when targets are repeated from previous trial ($F\{9,99\}=3.27$, $p<.01$). Response times were significantly faster in this condition in post-nicotine sessions compared with pre-

nicotine ($p<.05$). These effects did not survive Bonferroni correction for multiple comparisons.

Placebo effects during the nicotine week were demonstrated using analysis of variance on several variables. Mean reaction time when the target was repeated from previous trial ($F\{9,99\}=3.27$, $p<.01$); reaction times were faster post-placebo compared with pre-placebo session ($p<.05$, after Bonferroni correction). Mean reaction time when targets were presented in a different location to the previous trial ($F\{9,99\}=2.11$, $p<.05$) ; reaction times were faster post-placebo compared with pre-placebo session ($p<.001$, after Bonferroni correction). Mean reaction time when targets were presented alone ($F\{9,99\}=2.75$, $p<.01$); reaction times were faster post-placebo compared with pre-placebo session ($p<.001$, after Bonferroni correction). Mean reaction time responding to targets presented in the same location as the previous trial ($F\{9,99\}=3.23$, $p<.01$); reaction times were faster post-placebo compared with pre-placebo session ($p<.025$, this effect did not survive Bonferroni correction).

Mean reaction times where targets are in 'blank' (no distracter), 'far' and 'incompatible' (correct response key on opposite side to target) trials ($F\{9,99\}=2.35$, $p<.025$) ; reaction times were faster post-placebo compared with pre-placebo session ($p<.025$, after Bonferroni correction). Mean reaction time where targets were presented with a distracter, in the 'far' and 'incompatible' position ($F\{9,99\}=3.79$, $p<.001$); reaction times were faster post-placebo compared with pre-placebo session ($p<.01$, after Bonferroni correction). Mean reaction times to trials where a distracter is present, in the 'far' and 'compatible' condition ($F\{9,99\}=2.30$, $p<.025$); reaction

times were faster post-placebo compared with pre-placebo session ($p<.01$, this effect did not survive Bonferroni correction).

7A.2.1.3. Repeated digits RVIP/vigilance task

Two of the three global variables (mean total reaction time of responses, total number of 'hits' - correctly responding to a target 'repeat') measured by this task demonstrated a significant effect of session. The number of 'false alarms' (responses to non-targets) was not sensitive to session.

7A.2.1.3.1. Accuracy (RVIP)

7A.2.1.3.1.1. Withdrawal effect: comparison of baseline with pre-drug/ pre-placebo

Repeated measures analysis of variance showed a main effect of session on mean total number of hits on this task ($F\{9,99\}=3.12$, $p<.01$). Significantly more 'hits' were achieved in the baseline session than pre-drug session ($p<.05$) in the nicotine week. In the lofexidine week, significantly more 'hits' were made in the baseline session than in the pre-placebo session ($p<.025$). These effects do not survive Bonferroni correction for multiple comparisons.

7A.2.1.3.1.2. Lofexidine effect

Variables pertaining to accuracy on the repeated digits vigilance/RVIP task were shown to be not sensitive to effects of lofexidine in 24-hour tobacco withdrawn subjects. This was investigated using repeated measures analysis of variance to examine main effects of 'session', and Bonferroni corrected multiple comparisons of

estimated marginal means. No post-lofexidine sessions differed significantly from the pre-lofexidine sessions. No effects of placebo capsule were observed.

7A.2.1.3.1.3. Nicotine effect

Variables pertaining to accuracy on the repeated digits vigilance/RVIP task were shown to be not sensitive to effects of nicotine in 24-hour tobacco withdrawn subjects. This was investigated using repeated measures analysis of variance to examine main effects of 'session', and Bonferroni corrected multiple comparisons of estimated marginal means. No post-nicotine sessions differed significantly from the pre-nicotine sessions.

Analysis of variance demonstrated a placebo effect during the nicotine week on mean total number of hits ($F\{9,99\}=3.12$, $p<.01$). There was a greater number of 'hits' in the pre-placebo session than in the post-placebo session ($p<.001$, this marginally did not survive Bonferroni correction) (Figure 7.7 and Table 7.9).

7A.2.1.3.2. Reaction time (RVIP)

7A.2.1.3.2.1. Withdrawal effect: comparison of baseline with pre-drug/ pre-placebo

Withdrawal improves subjects' reaction times on this task. Repeated measures analysis of variance showed a main effect of session on total mean reaction time of responses on this task ($F\{9,99\}=2.94$, $p<.005$). Reaction time was significantly slower in the baseline session than the pre-drug session ($p<.05$) in the nicotine week. In the lofexidine week, reaction time was significantly slower in the baseline session compared to pre-placebo ($p<.05$). These effects do not survive Bonferroni correction.

7A.2.1.3.2.2. Lofexidine effect

Variables pertaining to reaction time on the repeated digits vigilance/RVIP task were shown to be not sensitive to effects of lofexidine in 24-hour tobacco withdrawn subjects. This was investigated using repeated measures analysis of variance to examine main effects of 'session', and Bonferroni corrected multiple comparisons of estimated marginal means. No post-lofexidine sessions differed significantly from the pre-lofexidine sessions. No effects of placebo capsule were observed.

7A.2.1.3.2.3. Nicotine effect

Variables pertaining to reaction time on the repeated digits vigilance/RVIP task were shown to be not sensitive to effects of nicotine in 24-hour tobacco withdrawn subjects. This was investigated using repeated measures analysis of variance to examine main effects of 'session', and Bonferroni corrected multiple comparisons of estimated marginal means. No post-nicotine sessions differed significantly from the pre-nicotine sessions.

Repeated measures analysis of variance showed a placebo effect on total mean reaction times of responses on this task ($F\{9,99\}=2.94$, $p<.005$). Faster reaction times were shown in the post-placebo session compared with pre-placebo ($p<.01$). This effect did not survive Bonferroni correction for multiple comparisons.

7A.2.2. Mood

7A.2.2.1. Alertness

Scores on this scale indicate general feelings of arousal, with high scores indicating greater alertness, and low scores expressing reduced alertness.

7A.2.2.1.1 Withdrawal effect: comparison of baseline with pre-drug/ pre-placebo

Pre-test alertness was affected by session as revealed by repeated measures analysis of variance ($F\{9,99\}=2.79$, $p<.01$). Pre-test alertness was rated significantly lower in pre-placebo ($p<.01$) and pre-drug ($p<.025$) sessions than baseline in the nicotine week (see Figure 7.8 and Table 7.10). These effects did not survive Bonferroni correction for multiple comparisons.

Post-test alertness was affected by session as revealed by repeated measures analysis of variance ($F\{9,99\}=2.3$, $p<.025$). Post-test alertness was rated significantly lower in pre-placebo ($p<.01$) and pre-drug ($p<.025$) sessions than baseline in the nicotine week. These effects did not survive Bonferroni correction for multiple comparisons.

There were no changes in alertness from pre- to post-test compared between baseline and withdrawn (pre-placebo and pre-drug) sessions in both nicotine and lofexidine weeks.

7A.2.2.1.2. Lofexidine effect

Repeated measures analyses of pre-test alertness and post-test alertness showed no lofexidine effects, as means did not differ significantly between pre-lofexidine and post-lofexidine sessions. No lofexidine placebo effects on pre-test alertness or post-test alertness were observed.

Alertness change scores between pre-test ratings in the pre-treatment session and post-test ratings in the post-treatment session were computed for lofexidine and placebo days. No significant differences were observed.

7A.2.2.1.3. Nicotine effect

Repeated measures analyses of pre-test alertness showed no nicotine effects, as means did not differ significantly between pre-nicotine and post-nicotine sessions. No nicotine placebo effects on pre-test alertness were observed.

Subjects rated their post-test alertness higher after administration of nicotine as shown by analysis of variance ($p<.025$), comparing pre-nicotine session with post-nicotine session (Figure 7.9, Table 7.11). Subjects also rated their post-test alertness significantly higher after administration of placebo inhalator as shown by analysis of variance, comparing pre-nicotine session with post-nicotine session ($p<.025$). These effects did not survive Bonferroni correction for multiple comparisons.

Alertness change scores between pre-test ratings in the pre-treatment session and post-test ratings in the post-treatment session were computed for nicotine and placebo days. No significant differences were observed.

7A.2.2.2. Hedonic tone

Higher ratings of hedonic tone indicate increased levels of positive affect and contentedness, whereas lower scores indicate negative attributes such as unhappiness and irritation.

7A.2.2.2.1. Withdrawal effect: comparison of baseline with pre-drug/ pre-placebo

Pre-test hedonic tone was affected by session as revealed by repeated measures analysis of variance ($F\{9,99\}=2.64$, $p<.01$). Pre-test hedonic tone was rated significantly lower than baseline in pre-placebo ($p<.05$) and pre-drug ($p<.05$) sessions in the lofexidine week (Figure 7.10 and Table 7.12), but this effect did not survive Bonferroni correction. A non-significant trend was observed for pre-test hedonic tone to also be rated lower than baseline in pre-placebo and pre-drug sessions in the nicotine week.

Post-test hedonic tone was affected by session as revealed by repeated measures analysis of variance ($F\{9,99\}=2.16$, $p<.05$). Post-test hedonic tone is rated significantly lower than baseline in pre-placebo ($p<.025$) and pre-drug ($p<.05$) sessions in the nicotine week, but these effects did not survive Bonferroni correction.

Changes in hedonic tone from pre- to post-test were not significantly affected by session.

7A.2.2.2.2. Lofexidine effect

Repeated measures analyses of pre-test hedonic tone and post-test hedonic tone showed no lofexidine effects, as means did not differ significantly between pre-lofexidine and post-lofexidine sessions. No lofexidine placebo effects on pre-test hedonic tone or post-test hedonic tone were observed.

Alertness change scores between pre-test ratings in the pre-treatment session and post-test ratings in the post-treatment session were computed for lofexidine and placebo days. No significant differences were observed.

7A.2.2.2.3. Nicotine effect

Repeated measures analyses of pre-test hedonic tone showed no nicotine effects, as means did not differ significantly between pre-nicotine and post-nicotine sessions. No nicotine placebo effects on pre-test hedonic tone were observed.

A non-significant trend was observed for subjects to rate their post-test hedonic tone higher in post-nicotine session compared with pre-nicotine session.

Subjects rated their post-test hedonic tone higher after administration of placebo inhalator as shown by ($p<.01$) comparing pre-placebo with post-placebo session (Figure 7.11 and Table 7.13), but this effect did not survive Bonferroni correction.

Hedonic tone change scores between pre-test ratings in the pre-treatment session and post-test ratings in the post-treatment session were computed for nicotine and placebo days. No significant differences were observed

7A.2.2.3. Anxiety

High scores on this scale indicate low anxiety, and vice versa (see Figure 7.12).

7A.2.2.3.1. Withdrawal effect: comparison of baseline with pre-drug/ pre-placebo

No significant withdrawal effects were indicated by analyses on visual analogue anxiety scales, although analysis of variance suggested a non-significant trend effect of session was emerging ($F\{9,99\}=1.8$, $p<.075$).

Analysis of variance revealed that post-test ratings of anxiety were not significantly affected by session.

Changes in anxiety from pre- to post-test were not significantly affected by session.

7A.2.2.3.2. Lofexidine effect

A repeated measures analysis of pre-test anxiety showed no lofexidine effect. Means did not differ significantly between pre-lofexidine and post-lofexidine sessions. No lofexidine placebo effects on pre-test anxiety were observed.

Ratings of post-test anxiety showed no lofexidine or placebo effect. Means did not differ significantly between pre-lofexidine and post-lofexidine sessions. Figure 7.12 shows mean post-test anxiety scores during the lofexidine week as an error-bar plot. The session means can also be viewed in Table 7.14.

Anxiety change scores between pre-test ratings in the pre-treatment session and post-test ratings in the post-treatment session were computed for lofexidine and placebo days. No significant differences were observed.

7A.2.2.3. Nicotine effect

A repeated measures analysis of pre-test anxiety showed no nicotine effect. Means did not differ significantly between pre-nicotine and post-nicotine sessions. No nicotine placebo effects on pre-test anxiety were observed.

Repeated measures analyses of variance on post-test anxiety showed no lofexidine effect. Means do not differ significantly between pre-lofexidine and post-lofexidine sessions. No lofexidine placebo effects on post-test anxiety were observed.

Anxiety change scores between pre-test ratings in the pre-treatment session and post-test ratings in the post-treatment session were computed for nicotine and placebo days. No significant differences were observed.

7A.3. Discussion (Section 7A)

The results above show that acute 24-hour tobacco abstinence has a variety of effects on cognitive performance and mood. These impairments are affected in different ways by nicotine and lofexidine, and performance tasks are not significantly affected by the different drugs in the same way. Withdrawal is shown to reduce response accuracy on all three cognitive performance tasks, whereas the effects on reaction time are equivocal. Lofexidine improved accuracy and reaction time performance on the categoric search task but had little impact on the other tests, while nicotine improved reaction time variables on the focused attention and categoric search tasks. Withdrawal reduced subjective ratings of alertness and hedonic tone. Lofexidine did not affect subjective mood ratings, but participants reported higher alertness and a trend toward higher hedonic tone following nicotine.

Cognitive performance

As predicted, withdrawal was shown to cause reductions in accuracy in the focused attention task, the categoric search task and the RVIP task. Conversely, nicotine withdrawal improved subjects' reaction times on the latter two tasks. These findings are not consistent with previous research, as Snyder, Davis & Heningfield (1989) showed that reaction times on attentional tasks were worsened by withdrawal and that accuracy was less affected. It may be that withdrawal induced a different performance style or strategy, or that withdrawn individuals during this study intentionally changed the equilibrium between speed and accuracy (i.e. performing tasks faster in order to smoke sooner).

Withdrawal was shown to reduce accuracy on focused attention task trials where either discordant or concordant distracter stimuli were presented 'near' to the target. This effect can be contrasted with differences in far-field stimuli, since the Eriksen effect (the relative interference effect of near-field distracters compared to far-field) was greater when subjects were in withdrawal. The finding that near-field non-targets were more distracting than far-field distracters suggests that the focus of attention had become narrowed by withdrawal.

Narrowing of the focus of attention is a phenomenon associated with increased frontal noradrenergic function. This theory is supported by cognitive performance studies using α2-antagonists; Smith et al. (1992a) showed that chronic idazoxan (an α2-antagonist causing increased levels of frontal noradrenaline) administration improved attentional performance as measured by the place repetition effect. Their subjects responded more quickly to targets presented in the same location as the previous trial

than one presented at a different location, suggesting a narrowing of focus of attention (Coull, 1994). The current results are also concordant with theories that withdrawal results in increased noradrenergic activity in the locus coeruleus (e.g. Redmond et al. 1977).

Withdrawal significantly reduced accuracy on focused attention task trials where the target was presented alone or with a neutral distracter. A similar withdrawal effect was observed on trials where targets are alternated from the previous trial. These kinds of errors may be due to transient changes in mood such as increased impulsiveness or impatience. As described in Chapter 4, impulsiveness is an established personality trait of dependent smokers (Mitchell, 1999) that may be intensified in conditions of withdrawal. Earlier research in the tobacco withdrawal syndrome (e.g. Hughes & Hatsukami, 1986) and DSM-IV cite "impatience" as a reliable symptom.

Subjects also performed less accurately in withdrawal on trials where the target was repeated from a previous trial. Together these results indicate a non-specific accuracy impairment, possibly explained by motor interference, or a more random, less attentive response style. To support this, it was shown that no reaction time variables on this task were affected by withdrawal. The trade-off between accuracy and reaction time associated with task performance appeared to change when in a state of withdrawal. Subjects were aware they would be able to smoke once the session was complete, therefore they may have been deliberately accelerating their performance, thus making more errors.

Accuracy and reaction time variables on the categoric search task were also sensitive to effects of 24-hour abstinence. Withdrawal impaired accuracy on trials where targets were presented alone, trials where targets were presented in the same location as the previous trial, and trials where targets were presented in a different location from the previous trial. The latter two results suggest that withdrawal does not differentially impair performance based on place repetition effects. This poses theoretical difficulties for a solely noradrenergic account of cognitive deficits associated with tobacco withdrawal. If withdrawal induced changes in noradrenergic function similar to α2-antagonists, significant place repetition effects would be predicted (Smith et al. 1992a). However, if subjects were responding randomly or impulsively, selective effects on place repetition may have been lost in a general accuracy deficit. Withdrawal effects were also seen when targets were presented with no distracter, in the 'far' position, with the correct response key in the 'incompatible' position. This may be attributable to impulsive responding, hitting the response key on the same side as the stimulus. Alternatively, it may again reflect a more random or less attentive response style.

Reaction time variables were more affected than accuracy by withdrawal in the categoric search task. Many reaction times were faster following 24-hour withdrawal. Again, subjects could be responding more quickly and therefore less accurately, reflecting either mood-based withdrawal symptoms such as impatience (see Section 7B) or a conscious attempt to finish tasks sooner in order to be able to smoke sooner. Interestingly, whereas reaction times on this task were faster in withdrawal than baseline (non-deprived), they were not affected on the focused attention task. If this

were singularly a result of changes in response style, the tasks would probably have been affected in similar ways.

Withdrawal effects were observed on variables measuring accuracy and response times on the repeated digits RVIP/vigilance task. Performance in terms of the number of 'hits' achieved during the task was worse than baseline following withdrawal in both weeks. This is consistent with previous studies; Sommese & Patterson (1995) found that tobacco abstinence adversely affected vigilance in airline pilots who smoked.

Lofexidine increased the time taken to encode a new response on the focused attention task, but improved accuracy and reaction time on the categoric search task. No lofexidine effect was observed on the RVIP task. Smith & Nutt (1996) reported clonidine having an adverse effect on sustained focused attention, which is analogous with the findings here.

In contrast, the relative improvement in categoric search task performance following lofexidine suggests that different attentional mechanisms are employed, possibly in a similar way to the Posner covert orientation of attention task (Posner, 1980). For example, reaction times were quicker on trials where targets were presented in the 'far' and 'incompatible' conditions with distracters following lofexidine. This may signal one of the direct effects of $\alpha 2$-agonists, a reduction in the interference of irrelevant stimuli. This would therefore be consistent with other work demonstrating $\alpha 2$-agonists broadening the focus of attention (Clark, Geffen & Geffen, 1989). If withdrawal does lead to increased frontal noradrenergic activity, and this mediates the

associated cognitive impairments, lofexidine (that reduces noradrenergic function) can to some extent reverse these deficits.

Nicotine administration reduced the Eriksen effect (spatial interference) on the focused attention task and improved reaction time on the categoric search task, but had no effect on the RVIP task. The beneficial effects of nicotine on attention in abstinent smokers are well documented, with administration shown to improve decision time on a choice reaction test (Bates et al. 1995) and improve reaction time in visual and auditory odd-ball tasks (Houlihan, Pritchard & Robinson, 1996). It is interesting that withdrawal increased spatial interference on the focused attention task whereas nicotine reduced it. Research in future could focus on whether the Eriksen effect is directly affected by nicotine, i.e. determine whether absolute effects can be observed in non-deprived smokers or non-smokers. The improvements following nicotine seen in the categoric search task are also consistent with previous research (Perkins et al. 1996).

The failure of nicotine to elicit effects on the RVIP task examined here is puzzling. Previous research has shown nicotine improves performance on RVIP tasks both via smoking (Wesnes & Warburton, 1983a; Gilbert, Estes & Welser, 1997) and NRT (Jones et al. 1992; Foulds et al. 1996; Mancuso et al. 1999). An insufficient dose is one possible reason for the lack of nicotine effect. Previous research indicates that one "puff" of an inhalator provides 13μg of nicotine at room temperature (Schneider et al. 1996). Although Schneider et al. (1996) state that this is based on shallow "puffing" rather than the deep inhalation used by participants in this research, it is still highly likely that blood levels of nicotine achieved were well below those attained by a

single cigarette. Mancuso et al. (1999) found improvements in RVIP performance after very small doses of nicotine administered via patch, although their levels were still likely to be higher than those attained in the current study. Different results may have been found if subjects had been allowed to use the inhalators *ad libitum* for (e.g.) a twenty-minute period.

Marked placebo effects were observed during the nicotine weeks. The placebo inhalator improved subjects' reaction times without affecting accuracy on the categoric search task. Placebo effects per se are well documented (Lasagna et al. 1954), and there is evidence that placebo NRT has considerable effects (Davies, Willner, James & Morgan, in press). It is interesting that the main placebo effect is analogous to the actual nicotine effect. This may be explained in terms of using the inhalator, simulating smoking. This contrasts with lofexidine, which is taken as a tablet (and is a novel substance rather than the desired drug). Simply performing the motor activity associated with delivering the drug of addiction could simulate neurochemical changes similar to actually obtaining the drug. Similar effects to this have been shown with other addictive substances, with sensory cues eliciting increased dopaminergic (reward) function (Schultz, 2001).

Mood

Withdrawal caused negative changes in mood, as predicted in the hypotheses. 24-hour abstinence from nicotine resulted in subjects rating their alertness and hedonic tone lower than when they were non-deprived. Tobacco withdrawal effects on alertness found here are consistent with previous research (e.g. Prosise et al, 1994), as drowsiness and daytime sleepiness are established symptoms of the syndrome.

Hedonic tone was also negatively affected by withdrawal. This is likely to be because the hedonic tone factor incorporated items such as 'sociability' and 'happiness'. Subjects increased irritability and negative affect were expressed on these scales, which is also consistent with previous formulations of withdrawal symptomatology (e.g. Hughes & Hatsukami, 1986).

Anxiety ratings were not significantly affected by 24-hour smoking abstinence, which was not predicted. A non-significant trend was observed, however, for subjects to register greater anxiety in the withdrawn sessions compared to baseline (non-deprived). Increased anxiety is a reliably demonstrated symptom of tobacco withdrawal (e.g. Hughes & Hatsukami, 1986; Hughes, 1992). It is possible these results failed to reach significance due to the structure of the Anxiety factor including less salient mood states. If specific individual items such as "Relaxed – Anxious" had been used, significance may have been reached.

Lofexidine failed to affect visual analogue mood ratings. It was expected that lofexidine would reduce anxiety and possibly reduce alertness, due its sedative side effect. These results differ to previous research, which has shown another α2-agonist (clonidine) to effectively reduce anxiety in tobacco-withdrawn smokers (Ornish et al. 1988; Prochazka et al. 1992). Although both pre- and post-test anxiety was rated lower following lofexidine, it failed to reach statistical significance, perhaps for the reasons outlined above. Alternatively, it may be that a single one-off dose may not have the anxiolytic efficacy of repeated exposures over a longer period (as utilised in the above studies).

Nicotine was shown to increase alertness, although the placebo inhalator elicited similar effects. This is consistent with previous findings, which found nicotine gum and smoking to increase ratings of arousal (Warburton et al. 1988; O'Neill & Parrott, 1992). Increased alertness may not be a direct effect of nicotine, a theory supported by the placebo effects. These may implicate the arousing effects of using the inhalator, or reflect neurochemical changes associated with smoking cues experienced by using the oral device (Schultz, 2001).

Methodological changes could be made to improve the study. Testing a larger number of subjects may have elicited more significant effects, and allowed more confident interpretation of results. It is clear that the impact of lofexidine and nicotine on both mood and cognitive performance in this design was limited. It would be useful to know whether the reason for this was insufficient doses of the two substances. This could be addressed by testing more subjects using higher doses; e.g. 0.4mg lofexidine and, most importantly, 20 minutes *ad libitum* use of the Nicorette© inhalator. This would provide levels of nicotine more analogous to smoking a cigarette (Schneider et al, 1996). It would have provided a useful variable if subjects had been asked to indicate whether they believed they had received placebo or drug in the post-administration sessions, so that expectancy effects could have been measured and possibly statistically controlled for.

There may have been important data lost in the way the mood factors were structures, perhaps through the inclusion of less salient mood states in each category. Since tobacco-withdrawn smokers are impatient, they may not have moved the cursor into its most appropriate or accurate position on the mood scales. Using pen-and-paper

visual analogue scales may have been more appropriate. Furthermore, there are ongoing debates as to the precision or suitability of bi-polar mood scales as opposed to uni-polar scales. Bi-polar scales assume that the words given are genuine opposites in 'mood space', rather than antonyms as heuristics of psychological state.

Tobacco withdrawal was shown to impair cognitive performance and cause negative changes in mood states. Lofexidine and nicotine can reverse some of these deficits, though they seem to affect different aspects to each other. Withdrawal reduced accuracy on the focused attention, vigilance/RVIP and categoric search tasks. Reaction times were often faster in withdrawal sessions, and these changes were either a direct neuropsychological result of withdrawal, or subjects were intentionally performing with a faster (and less accurate) strategy in order to be able to smoke sooner. Lofexidine improved subjects' accuracy and reduced the impact of distracters on reaction times in the categoric search task, but had no positive effect on performance in the focused attention or RVIP task. Nicotine was shown to improve reaction times on the focused attention task and categoric search task, although the latter also showed many placebo effects. Contrary to previous work, nicotine did not affect performance on the RVIP task. Visual analogue ratings of alertness and hedonic tone were reduced following 24-hour tobacco withdrawal. Lofexidine made no impact on these ratings, whereas nicotine significantly increased ratings of alertness and hedonic tone. Even at the low levels used here, nicotine still appeared to be effective at reducing withdrawal-induced mood deficits, while lofexidine might be examined in tandem with nicotine in terms of cognitive deficit reversal.

SECTION 7B

7B.1. Statistical analyses

See section 7A.1. for rationale rejecting using 2x2 factorial ANOVA model. Repeated measures analysis of variance was carried out on the performance data using SPSS 9.0 statistical package. Due to the large number of comparisons, session means contrasts were examined using Bonferroni correction for multiple comparisons. WSC and OWS data were analysed both as summed totals and appropriate individual items from each questionnaire. QSU data was reduced to factor scores based on the original Tiffany & Drobes (1991) two-factor structure. POMS data was also reduced to factor scores, yielding measures of Anger, 'Vigour', 'Tension', 'Confusion', Depression and Fatigue.

7B.2. Results

7B.2.1. Withdrawal Symptoms Checklist

Withdrawal symptoms ratings on the WSC were totalled to give a total severity of tobacco withdrawal score. These were examined using repeated measures analysis of variance with Bonferroni correction for multiple comparisons. The most sensitive items (as indicated by Hughes & Hatsukami, 1986) and those most likely to indicate acute drug effects were also examined individually.

7B.2.1.1. Withdrawal effects on WSC scores

Total WSC scores were analysed and a main effect of session was demonstrated ($F[9,99]=9.92$, $p<.001$). Both pre-placebo ($p<.01$) and pre-drug ($p<.05$) (i.e. withdrawn) sessions had higher WSC totals than baseline (non-deprived) in the nicotine week. Similarly, pre-placebo ($p<.01$) and pre-drug ($p<.01$) sessions had

higher WSC totals than baseline in the lofexidine week (Figure 7.13 and Table 7.15). These effects survived Bonferroni correction for multiple comparisons.

'Craving for tobacco' demonstrated a main effect of session ($F[9,99]=15.16$, $p<.01$), with pre-placebo ($p<.001$) and pre-drug ($p<.001$) sessions significantly higher than baseline in the nicotine week. Pre-drug ($p<.01$) and pre-placebo ($p<.001$) sessions were significantly higher than baseline in the lofexidine week (these significance levels were using Bonferroni correction for multiple comparisons). 'Anxiety' WSC ratings were also affected by session ($F[9,99]=3.03$, $p<.01$), with pre-placebo session mean ratings in the nicotine week significantly higher than baseline ($p<.05$, after Bonferroni correction). 'Impatience' was affected by session as revealed by analysis of variance ($F[9,99]=8.49$, $p<.001$). After Bonferroni correction, ratings were significantly higher than baseline in pre-placebo ($p<.001$) and pre-drug ($p<.05$) sessions in the nicotine week. 'Impatience' was also rated higher than baseline in pre-drug sessions ($p<.05$) and pre-placebo sessions ($p<.05$) in the lofexidine week, after Bonferroni correction.

7B.2.1.2. Lofexidine effects on WSC scores

Post-lofexidine session WSC totals were significantly lower than pre-lofexidine means ($p<.025$) (Figure 7.13). There was a non-significant trend ($p=.054$) for 'Craving for tobacco' to be lower in the post-lofexidine session than pre-lofexidine. 'Anxiety' was lower in the post-lofexidine session than pre-lofexidine ($p<.05$) (Figure 7.14). Subjects' ratings of 'impatience' were lower in the post-lofexidine session than pre-lofexidine ($p<.01$). None of the above effects survived Bonferroni correction for multiple comparisons.

7B.2.1.3. Nicotine effects on WSC scores

When total WSC scores were compared between the sessions using repeated measures analysis of variance, there was no significant difference between pre-nicotine and post-nicotine sessions, with or without Bonferroni correction. However, nicotine effects could be observed when WSC items were analysed individually. 'Craving for tobacco' was significantly reduced by the administration of nicotine (pre-nicotine versus post-nicotine, $p<.01$). This effect narrowly failed to survive Bonferroni correction ($p=.069$). There was also a significant effect of placebo on 'craving for tobacco' during the nicotine week (pre-placebo v post-placebo session, $p<.05$). A non-significant trend was observed ($p=.053$) for subjects to rate 'anxiety' lower following administration of nicotine (pre- vs. post-nicotine sessions). Subjects rated 'impatience' lower following administration of the placebo inhalator ($p<.05$). These effects did not survive Bonferroni correction for multiple comparisons.

7B.2.2. Other Withdrawal Symptoms

Withdrawal symptoms ratings on the OWS were totalled to give a total of opiate-like withdrawal score. These were examined using repeated measures analysis of variance with Bonferroni correction for multiple comparisons. The most appropriate items on the OWS, reflecting those indicating noradrenergic involvement (as indicated by various sources including Hughes & Hatsukami, 1986) were also examined individually. Appropriate individual items with significant effects of withdrawal, lofexidine or nicotine action are reported.

7B.2.2.1. Withdrawal effects on OWS scores

Total OWS ratings differed according to session as revealed by repeated measures analysis of variance ($F[9,99]=5.29$, $p<.001$). Withdrawal effects were observed as pre-placebo OWS were significantly higher than baseline totals in the lofexidine week ($p<.05$, after Bonferroni correction for multiple comparisons). Pre-placebo ($p<.01$) and pre-drug ($p<.05$) sessions had significantly higher OWS totals than baseline in the nicotine week. In the lofexidine week, total OWS were significantly higher in pre-drug ($p<.01$) or pre-placebo ($p<.001$) sessions than in baseline. Aside from the latter contrast, these effects did not survive Bonferroni correction.

Scores of 'Excessive yawning' were affected by session ($F[9,99]=2.66$, $p<.01$). Withdrawal effect was demonstrated by significantly higher than baseline scores in pre-drug sessions ($p<.05$) in the nicotine week; and by significantly higher than baseline scores in pre-placebo sessions ($p<.05$) in the lofexidine week. 'Trouble getting to sleep' ratings were also significantly affected by session ($F[9,99]=3.36$, $p<.001$), and was rated higher in the pre-drug session than the baseline in the lofexidine week ($p<.01$). 'Runny nose' was significantly affected by session ($F[9,99]=2.07$, $p<.05$). Pre-drug ratings were significantly higher than baseline in the nicotine week ($p<.05$), although the nicotine week baseline was significantly lower ($p<.05$) than the lofexidine week baseline. These effects did not survive Bonferroni correction for multiple comparisons.

'Excessive sweating' was also demonstrated to be affected by session ($F[9,99]=2.00$, $p<.05$). Ratings were significantly higher than baseline in pre-placebo sessions in both the nicotine week ($p<.05$) and lofexidine week ($p<.05$). Feeling 'tense and jittery' was

sensitive to session effects (F[9,99]=3.32, p<.001), with ratings being significantly higher than baseline in the pre-placebo (p<.01) and pre-drug (p<.05) sessions in the nicotine week. In the lofexidine week, ratings were significantly higher in both the pre-drug (p<.05) and pre-placebo (p<.05) session than in baseline. A main effect of session on mean ratings of 'watery eyes' (F[9,99]=2.43, p<.025) was found. Subjects rated 'watery eyes' significantly higher following withdrawal than in the baselines, as differences between baseline and pre-placebo ratings in the nicotine week (p<.05), and between baseline and pre-drug sessions in the lofexidine week (p<.01) demonstrated. These effects did not survive Bonferroni correction for multiple comparisons.

'Fitful sleep' (F[9,99]=3.11, p<.01), 'bothered by noises' (F[9,99]=2.72, p<.01) and 'skin clammy and damp' (F[9,99]=2.33, p<.05) were further items with ratings significantly affected by session. These showed various profiles of differences between baseline and withdrawal during the two experimental weeks. In all cases, ratings of these symptoms were significantly higher during the withdrawn sessions compared to baseline. These effects do not survive Bonferroni correction for multiple comparisons.

7B.2.2.2. Lofexidine effects on OWS scores

Subjects OWS totals were significantly lower following lofexidine administration (mean total OWS pre- versus post-lofexidine, p<.05). OWS were also significantly reduced by placebo capsule (pre-placebo versus post-placebo, p<.05). These effects did not survive Bonferroni correction for multiple comparisons.

Lofexidine caused no significant changes in the individual OWS items. Lofexidine placebo was related to a reduction in ratings of 'excessive sweating' by significant differences between pre- and post-placebo means ($p<.05$).

7B.2.2.3. Nicotine effects on OWS scores

Nicotine administration significantly lowered subjects total OWS ratings (pre- versus post-nicotine, $p<.025$). This effect did not survive Bonferroni correction for multiple comparisons.

Mean ratings of 'runny nose' were significantly lower in post-nicotine session compared with pre-nicotine ($p<.05$). The effect did not survive Bonferroni correction for multiple comparisons.

There was also a placebo effect during the nicotine week on subjects ratings of 'tense and jittery' feelings, as post-placebo mean ratings were significantly lower than pre-placebo ratings ($p<.05$). These effects did not survive Bonferroni correction for multiple comparisons.

7B.2.3. Combining and contrasting WSC and OWS scores

Withdrawal symptoms total scores were computed for each subject for each session by totalling items on both the WSC and OWS. These were then analysed using SPSS repeated measures analysis of variance, with Bonferroni correction for multiple comparisons.

WSC/OWS combined total scores were rated higher in all sessions after 24-hour withdrawal compared to baseline (Table 7.15). Repeated measures analysis of variance revealed a main effect of session ($F[9,99]=7.57$, $p<.001$), with WSC/OWS totals significantly higher than baseline in the pre-placebo session ($p<.05$, after Bonferroni correction) in the nicotine week. This effect was repeated during the lofexidine week, as pre-placebo ($p<.01$) and pre-drug sessions ($p<.05$) had higher total withdrawal (WSC/OWS) than baseline. All these contrasts survived Bonferroni correction.

The relationship between OWS and WSC was demonstrated by comparing line graphs of mean total responses for the two questionnaires across the sessions (Figure 7.14). Furthermore, session means for the WSC and OWS were compared using Spearman's Rho correlation (see Table 7.16), with some sessions correlating significantly.

7B.2.4. Questionnaire of Smoking Urges (QSU)

The original Tiffany & Drobes (1991) two-factor structure was utilised, as this sample was too small to reliably perform a novel principal components analysis. Factor scores were created for Factor 1 (appetitive desire to smoke) and Factor 2 (seeking withdrawal reversal) for each subject (n=12) in each session (10). A repeated measures analysis of variance was then performed. The means for each session can be viewed in tables 7.17 (Factor 1) and 7.18 (Factor 2).

Analysis of variance revealed a main effect of session for Factor 1 scores ($F[9,99]=18.13$, $p<.001$) and Factor 2 scores ($F[9,99]=10.23$, $p<.001$).

7B.2.4.1. Withdrawal effects on QSU

Baseline mean Factor 1 scores were shown to differ significantly from both pre-placebo ($p<.001$) and pre-drug ($p<.001$) scores in the nicotine week. In the lofexidine week, Factor 1 scores differed significantly between baseline and both pre-drug ($p<.001$) and pre-placebo ($p<.001$) sessions. QSU Factor 1 scores were much lower in baseline sessions than withdrawn sessions (Table 7.17), showing that subjects' appetitive desire to smoke was greater after 24-hour abstinence than when they were non-deprived.

A similar effect was observed for Factor 2. Baseline mean Factor 2 scores were shown to differ significantly from both pre-placebo ($p<.001$) and pre-drug ($p<.001$) scores in the nicotine week. In the lofexidine week, Factor 2 scores differed significantly between baseline and both pre-drug ($p<.01$) and pre-placebo ($p<.01$) sessions. QSU Factor 2 scores were much lower in baseline sessions than withdrawn sessions (Table 7.18), showing that subjects' urges to smoke in order to alleviate perceived withdrawal symptoms was greater after 24-hour abstinence than when they were non-deprived.

7B.2.4.2. Lofexidine effects on QSU scores

Factor 1 scores were significantly reduced following lofexidine (pre-lofexidine versus post-lofexidine sessions $p<.05$), although this effect did not survive Bonferroni correction. No significant effect of lofexidine was demonstrated in Factor 2 scores.

7B.2.4.3. Nicotine effects on QSU scores

Although nicotine administration reduced QSU scores, there were no significant effects on either Factor, with or without Bonferroni correction.

7B.2.5. Profile Of Mood States (uni-polar)

POMS responses generate scores on five factors: Anger, 'Tension', Depression, 'Vigour', Fatigue and 'Confusion'. Significant main effects of session were observed on the factor scores for 'Tension' ($F[9,81]=2.92$, $p<.005$) (Table 7.19), 'Vigour' ($F[9,81]=2.69$, $p<.01$) (Table 7.20) and 'Confusion' ($F[9,81]=3.88$, $p<.001$) (Table 7.21).

7B.2.5.1. Effect of 24-hour nicotine withdrawal on POMS

'Confusion' factor scores were significantly higher than baseline in both pre-placebo ($p<.01$) and pre-drug ($p<.05$) sessions in the nicotine week. In the lofexidine week pre-drug session ($p<.05$) 'Confusion' scores were higher than baseline. These effects did not survive Bonferroni correction.

'Vigour' mean scores were lower than baseline in the pre-drug session in the nicotine week ($p<.05$). This effect did not survive Bonferroni correction for multiple comparisons.

'Tension' factor scores were significantly higher in both pre-placebo ($p<.05$) and pre-drug ($p<.01$) sessions in the nicotine week. In the lofexidine the pre-drug session 'Confusion' factor scores were higher than baseline ($p<.05$). These effects did not survive Bonferroni correction.

7B.2.5.2. Effect of lofexidine administration on POMS

Lofexidine administration had no significant effect on 'Confusion' factor scores (comparing pre- and post-lofexidine means).

'Vigour' factor scores were rated much lower following the administration of lofexidine, as pre- and post-lofexidine sessions were significantly different ($p<.05$). This effect did not survive Bonferroni correction.

'Tension' factor scores were significantly lower following lofexidine administration (pre- versus post-lofexidine session, $p<.05$). This effect did not survive Bonferroni correction for multiple comparisons.

7B.2.5.3. Effect of nicotine administration on POMS

The administration of nicotine had no significant effect on subjects' ratings of 'Confusion', 'Vigour' or 'Tension'. Nicotine placebo significantly reduced 'Tension' factor scores (pre-placebo versus post-placebo session, $p<.05$), although this did not survive Bonferroni correction.

7B.3. Discussion (Section 7B)

Acute 24-hour abstinence from smoking was shown to induce an array of characteristic withdrawal symptoms (tobacco withdrawal syndrome), as measured by a Withdrawal Symptoms Checklist. These are concordant with previous findings (e.g. Hughes & Hatsukami, 1986), and the similar response pattern with a checklist of opiate-like withdrawal symptoms suggests tobacco withdrawal may have noradrenergic components. Withdrawal also reliably increased cravings and urges to

smoke (measured by Questionnaire of Smoking Urges; Tiffany & Drobes, 1991), and caused negative changes in mood state (reduced 'Vigour' scores, increased 'Tension' and 'Confusion' scores on the Profile of Mood States; McNair et al. 1971, 1981). An oral dose of 0.2mg lofexidine reduced urges to smoke and POMS scores on 'Tension' and 'Vigour' factors. It also reduced severity ratings of withdrawal symptoms on both WSC and OWS, particularly anxiety, impatience and excessive sweating. Its effects are more marked than nicotine, which (by this dose and means of administration) has not been shown to affect urges to smoke measured by QSU or significantly alter POMS acute mood states in 24-hour nicotine withdrawn subjects. However, the nicotine inhalator was found to reduce craving for tobacco and runny nose better than placebo measured using the WSC and OWS respectively.

Withdrawal symptoms following 24-hour abstinence from smoking were rated significantly higher than baseline (non-deprived), as predicted. Totals on WSC and OWS were greater following withdrawal than in the baseline sessions. Items that are robust symptoms of the tobacco withdrawal syndrome such as 'craving for tobacco', 'anxiety' and 'impatience' were rated higher following withdrawal. This finding is consistent with previous research using the WSC (Hughes & Hatsukami, 1986).

Withdrawal clearly affected subjects' sleep quality, as 'trouble getting to sleep', 'fitful sleep' and 'excessive yawning' (inter-related OWS items) were all rated higher in withdrawn sessions. Interestingly, subjects rated OWS items 'runny nose', 'watery eyes', 'excessive sweating' and 'skin clammy and damp' higher following withdrawal. These symptoms are strongly associated with the excessive frontal noradrenergic activity typical of opiate withdrawal (Strang, Bearn & Gossop, 1999).

This would support the theory that nicotine withdrawal produces similar increases in noradrenaline to opiate withdrawal, albeit less severe. Alternatively these symptoms may be secondary, perhaps associated with insufficient sleep.

Smoking urges, as measures by Tiffany & Drobes (1991) questionnaire were markedly increased as a result of 24-hour abstinence. Using the authors' original 2-factor structure, the results indicate that withdrawal increased both Factor 1 (primary intention and desire to smoke, and anticipated pleasure) and Factor 2 (anticipation of relief from negative affect and withdrawal) scores. These results are consistent with Tiffany & Drobes (1991) and subsequent validations (e.g. Morgan, Davies & Willner, 1999). Although Tiffany & Drobes (1991) studied a general public sample, it was demonstrated that the original factor structure could be appropriately applied to this mainly student sample.

'Confusion', 'Vigour' and ''Tension'' were factors of the Profile of Mood Sates (McNair et al. 1971; 1981) that were significantly affected by 24-hour abstinence. Subjects rated items on the 'Confusion' factor significantly higher than the appropriate baseline session in three of the four withdrawn sessions. Subjects may have rated salient items (e.g. 'muddled' and 'bewildered') highly during withdrawal to express their perceived difficulty concentrating or attentional problems (Hughes & Hatsukami, 1986; Snyder, Davis & Heningfield, 1989). Items loading on the 'Tension' factor were also rated higher in three of the four withdrawn sessions comparative to baseline. This is likely to reflect withdrawal symptoms such as impatience, anxiety and irritability (e.g. Hughes & Hatsukami, 1986). 'Vigour' factor effects were less reliable, as just one withdrawn session was significantly lower than

baseline, although factor scores were lower than baseline in all sessions. This may be related to sleep disturbance, or reduced feelings of general arousal directly due to nicotine withdrawal. The latter explanation is supported, since if subjects were suffering from tiredness Fatigue ratings would have been significantly higher following withdrawal.

The administration of lofexidine caused acute changes in severity ratings of withdrawal symptoms. WSC totals were significantly lower in the post-lofexidine session compared with pre-lofexidine, suggesting that lofexidine has a generally alleviating effect on tobacco withdrawal symptoms measured by this instrument. This is a novel finding, but is consistent with studies showing that the lofexidine analogue clonidine can ameliorate tobacco withdrawal (Prochazka et al. 1992). Total OWS scores were also significantly reduced by lofexidine; these items were included to measure more defined noradrenergic withdrawal effects. It was expected that OWS would be more affected by lofexidine than WSC, which was not shown. Furthermore, the fact that placebo was as effective at reducing total OWS as lofexidine may indicate that nicotine withdrawal is only moderately mediated by noradrenaline.

Although only a trend, WSC item 'craving for tobacco' was rated lower following lofexidine. This may have reached significance had there been greater numbers of subjects. This finding is important; as it suggests that lofexidine could be used to ameliorate tobacco withdrawal pharmacotherapeutically in those attempting to quit. This result is comparable to the equivocal findings of studies examining clonidine and craving for tobacco (e.g. Ornish et al. 1988, showed a reduction in craving; Murray et al. 1989, showed no reduction). Other WSC items also rated lower following

lofexidine were 'impatience' and 'anxiety'. Alleviation of anxiety is a robust effect of this dose of lofexidine (Aghajanian, 1978; Uhde et al. 1980), and other α2-agonists have been shown to reduce the anxiety component of tobacco withdrawal (e.g. Prochazka et al. 1992). The observed reduction of impatience may be a secondary effect of the amelioration of anxiety or the sedative side effect.

Subjects rated items loading on Factor 1 (primary intention and desire, or positive reinforcement) of the QSU significantly lower after administration of lofexidine. Reductions in scores on Factor 2 (withdrawal-removal motivation, or negative reinforcement) following lofexidine were expected but not observed. When considered in conjunction with the trend of lofexidine reducing 'craving for tobacco', it seems that the drug somehow decreases the positive reinforcement urges to smoke rather than perceived withdrawal alleviation. This result is difficult to explain in the context of withdrawal symptom amelioration effected by lofexidine in this study, and the similar effects of clonidine on withdrawal symptoms in previous studies (e.g. Prochazka et al. 1992). This finding may have implications for the QSU, as it suggests that the 2-factor structure does not adequately define the items in the instrument. Perhaps Factor 2 includes too many items not directly relating to "withdrawal-removal" motivations. An alternative explanation is that the actual symptoms experienced are not the same as those expected to be relieved by smoking. This idea requires further investigation, since it would change the conceptualisation of the tobacco withdrawal syndrome.

'Vigour' and 'Tension' POMS factors were significantly affected by lofexidine. Subjects' ratings of 'Vigour' items were reduced by the administration of lofexidine.

This is likely to reflect the sedative side effects of the drug (e.g. Akhurst, 1999). 'Tension' factor scores were also reduced by lofexidine. This result was ascribable to the anxiolytic and/or sedative effects of lofexidine, reducing ratings of items such as 'nervous' and 'uneasy'. This provides further evidence for lofexidine targeting the 'panic-anxious' component of a withdrawal syndrome (Uhde et al. 1980). The sedative side effects of lofexidine are less prominent than with clonidine, but may be problematic if attempting to use the drug to assist smoking cessation either by itself or as an adjunct to NRT. Clinical trials would need to be run to establish whether individuals in nicotine withdrawal could become tolerant to the sedative effects.

OWS total scores were lower following the administration of nicotine, and this effect was not observed with the placebo inhalator. Individual WSC items were sensitive to the effects of nicotine, although total WSC scores were not significantly altered. 'Craving for tobacco' was significantly lower following nicotine administration, and there was a non-significant trend for subjects to rate 'anxiety' lower after receiving nicotine. This is consistent with previous research (e.g. West & Shiffman, 2001). Placebo inhalator significantly reduced ratings on 'craving for tobacco' and 'impatience' items. Administration of nicotine also reduced subjects' ratings of the OWS item 'runny nose'. This may be a genuine withdrawal reversal effect, or possibly the alleviation effect of nicotine on anxiety and irritability combined with the trigeminal nerve stimulation effected by the menthol had misled subjects into thinking their noses were less runny.

QSU scores on both Factors were unaffected by nicotine, contrary to predictions. This is not consistent with other research that suggests NRT can reduce QSU ratings (Allen

et al. 2000). This again suggests that the dose of nicotine delivered by eight puffs on the inhalator was too low to have a measurable effect. Nicotine was shown to have no statistically significant effect on POMS factor scores. This finding was not predicted, and is inconsistent with previous studies (e.g. Hughes et al. 1984). This may again reflect too low a dose of nicotine to achieve reliable effects. There was a placebo effect on 'Tension' factor scores, with subjects rating their ''Tension'' lower following the non-nicotine inhalator. This is explained in terms of subjects simulating smoking behaviour, with the cues leading to neurochemical and mood changes analogous to actually receiving the drug (Scultz, 2001).

This study demonstrated that 24-hour smoking abstinence caused an increase in ratings of withdrawal measured using two symptom checklists (WSC and OWS) that generally correlated with each other. Abstinence also led to higher ratings of urge to smoke (measured by QSU) and increased ratings on POMS 'Confusion' and 'Tension' factors, and reduced ratings on POMS 'Vigour' factor. Lofexidine administered to withdrawn subjects reduced severity ratings of withdrawal symptoms, reduced appetitive urges and primary intention to smoke, and reduced POMS 'Vigour' and 'Tension' scores. Nicotine also reduced severity ratings of withdrawal symptoms, but did not affect urges to smoke measured by the QSU. NRT also failed to alter any POMS factor scores. Although both substances mitigated withdrawal effects and tobacco craving, they appeared to affect different aspects of the syndrome.

GENERAL DISCUSSION

7.3. General Discussion

The results of sections 7A and 7B present a case for further investigation of the effects of lofexidine on nicotine withdrawal. 24-hour abstinence from smoking was shown to cause impairments in cognitive performance, adversely affect mood and increase urges to smoke.

The administration of lofexidine improved specific aspects of withdrawal-impaired cognitive performance, but did not affect mood states measured by visual analogue scales, including performance-related Anxiety. However, other mood measures used showed significant reductions in anxiety ('Tension'), illustrating the value of utilising more than one mood measure instrument. Alertness ('Vigour') variables and severity ratings of withdrawal symptoms were also reduced following lofexidine. Positive reinforcement (appetitive) urges to smoke were reduced following lofexidine administration, although urges pertaining to negative reinforcement (anticipation of relief from withdrawal effects) were not affected. NRT improved some reaction time variables of cognitive performance, and significantly increased alertness measured by visual analogue scales. Again, the VAS mood data was inconsistent with the Likert (POMS) mood data, as these were unaffected by nicotine administration. Nicotine was also shown to reduce withdrawal symptoms induced by 24-hour abstinence.

Both nicotine and lofexidine were shown to reverse some of the effects of withdrawal on the mood and questionnaire data. There was moderate overlapping of the individual cognitive performance variables affected by the three conditions. In the context of the withdrawal relief afforded by both lofexidine and NRT as demonstrated

by the WSC and OWS, the cognitive performance findings are confusing. There are several potential explanations of these various anomalies. It could be that the improvements in cognitive performance following lofexidine or nicotine administration are not actually a result of withdrawal reversal, but a psychological response to a novel behaviour or mental state.

The weak effects of both substances may suggest that the doses (particularly nicotine) used in this study were too low. The inhalator method of NRT was chosen primarily because it is the most analogous to smoking, with similar kinaesthetic qualities and motor actions required. The actual nicotine dose administered by eight puffs of an inhalator was unknown and subject to individual variation, but was likely to have been very low. This dose was estimated from the information provided with the Nicorette© device. Future studies should use a longer period of *ad libitum* use to allow subjects to freely increase their plasma nicotine. Using a higher dose of lofexidine may also have elicited greater effects, although this is more problematic. In lofexidine-naïve individuals it is possible that 0.4mg may act post-synaptically, increasing noradrenergic function. If tobacco withdrawal symptoms are in some way related to increased noradrenergic activity (perhaps in the locus coeruleus) then lofexidine acting post-synaptically could exacerbate the relevant phenomena rather than attenuate them.

The moderate reversal of cognitive performance decrements and the reduction in withdrawal symptoms and smoking urges associated with lofexidine represents an interesting and exciting development in tobacco withdrawal research. Although similar work has been undertaken with clonidine (Prochazka et al. 1992), lofexidine

has fewer hypotensive and sedative side effects (Gerra et al. 2001). The results presented in this chapter state a case for further investigation of the effects of lofexidine on nicotine withdrawal. Future studies should examine lofexidine and NRT concurrently as possible adjunctive pharmacotherapy. These findings also support a contribution of noradrenaline to the tobacco withdrawal syndrome.

Figure 7.1 Graph showing mean accuracy of responses to targets presented alone or with asterisks on the focused attention task in the lofexidine week.

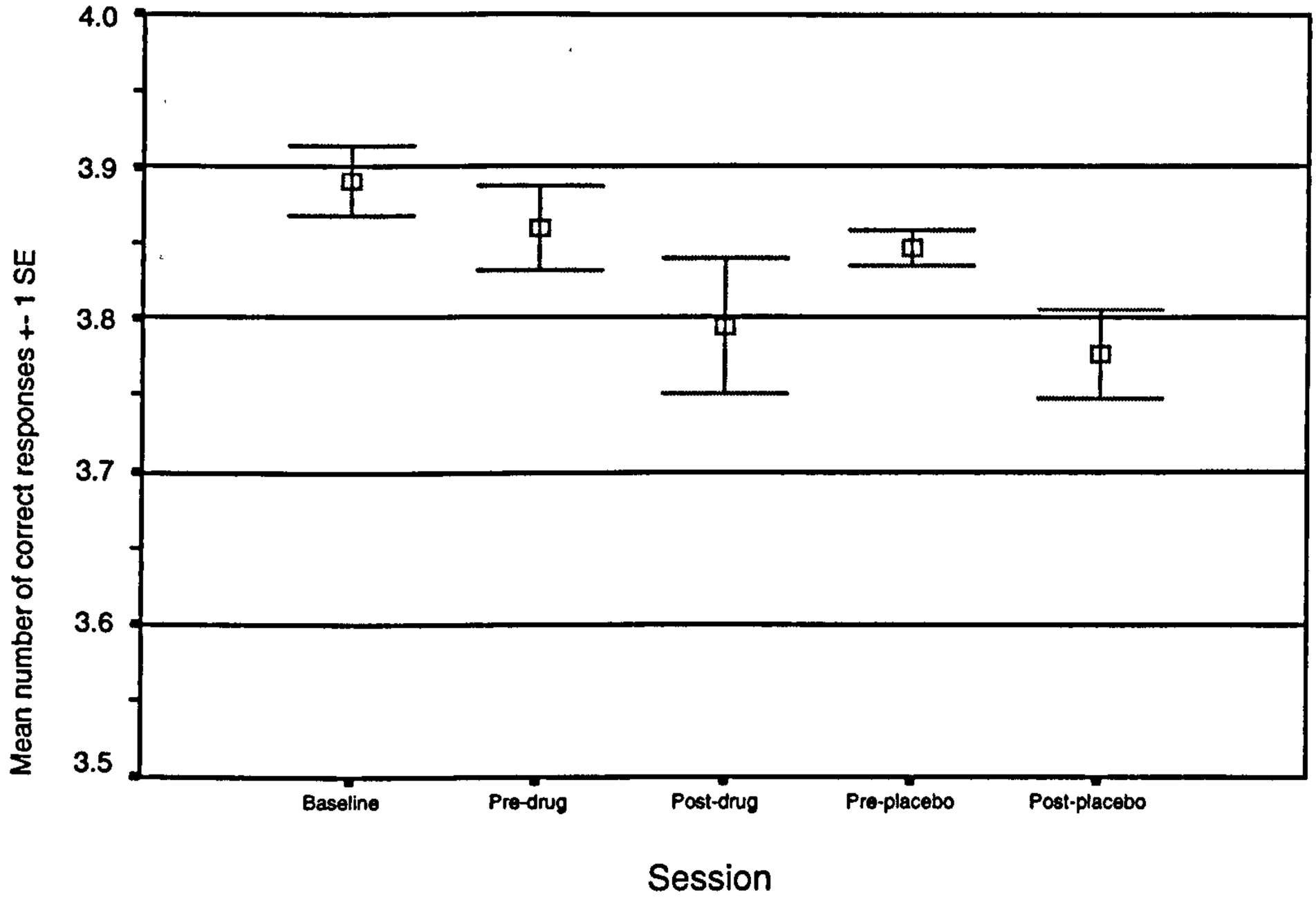


Figure 7.2 Graph showing mean accuracy of responses to targets alternating from previous trial on the focused attention task in the lofexidine week.

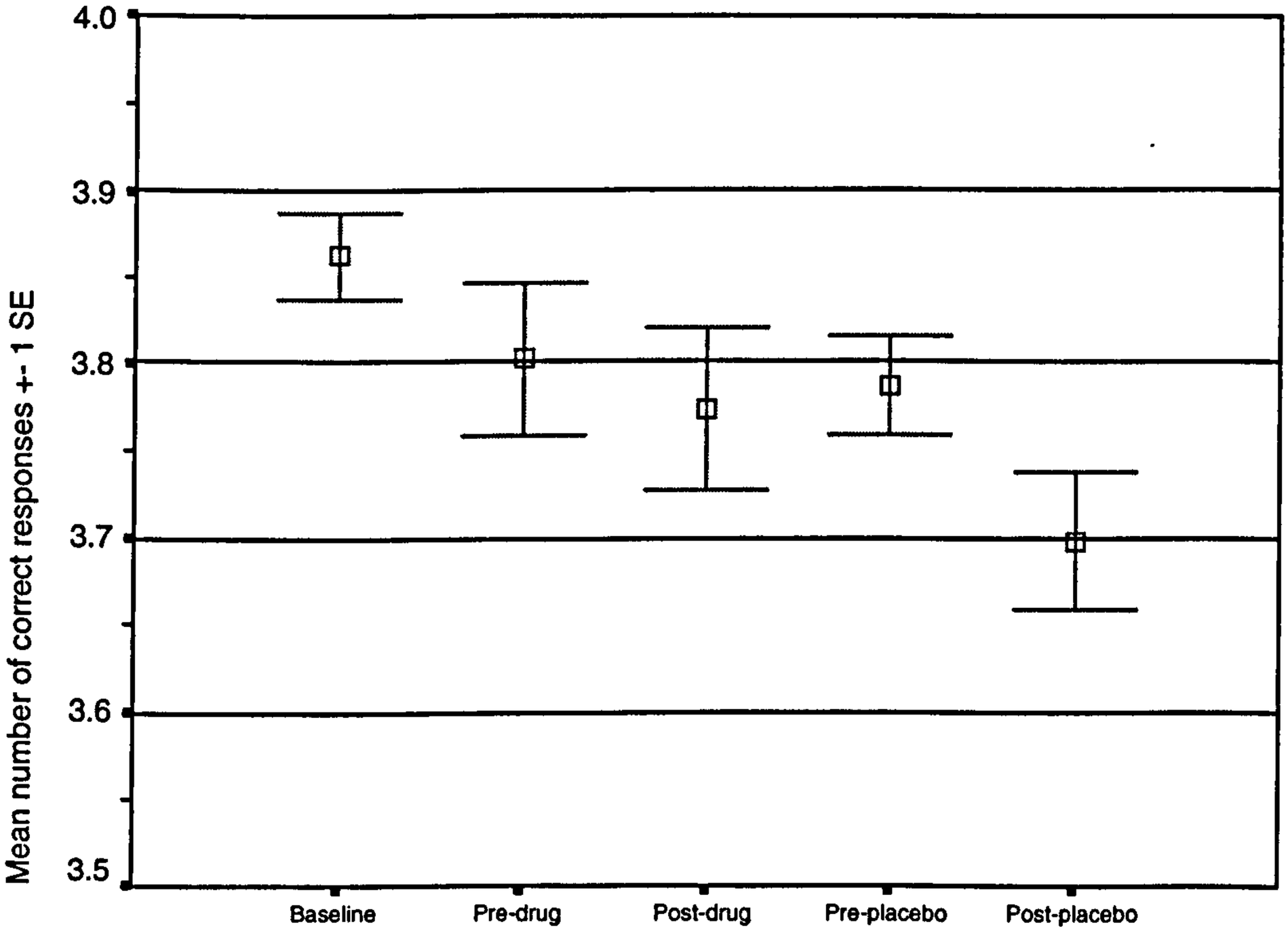


Figure 7.3

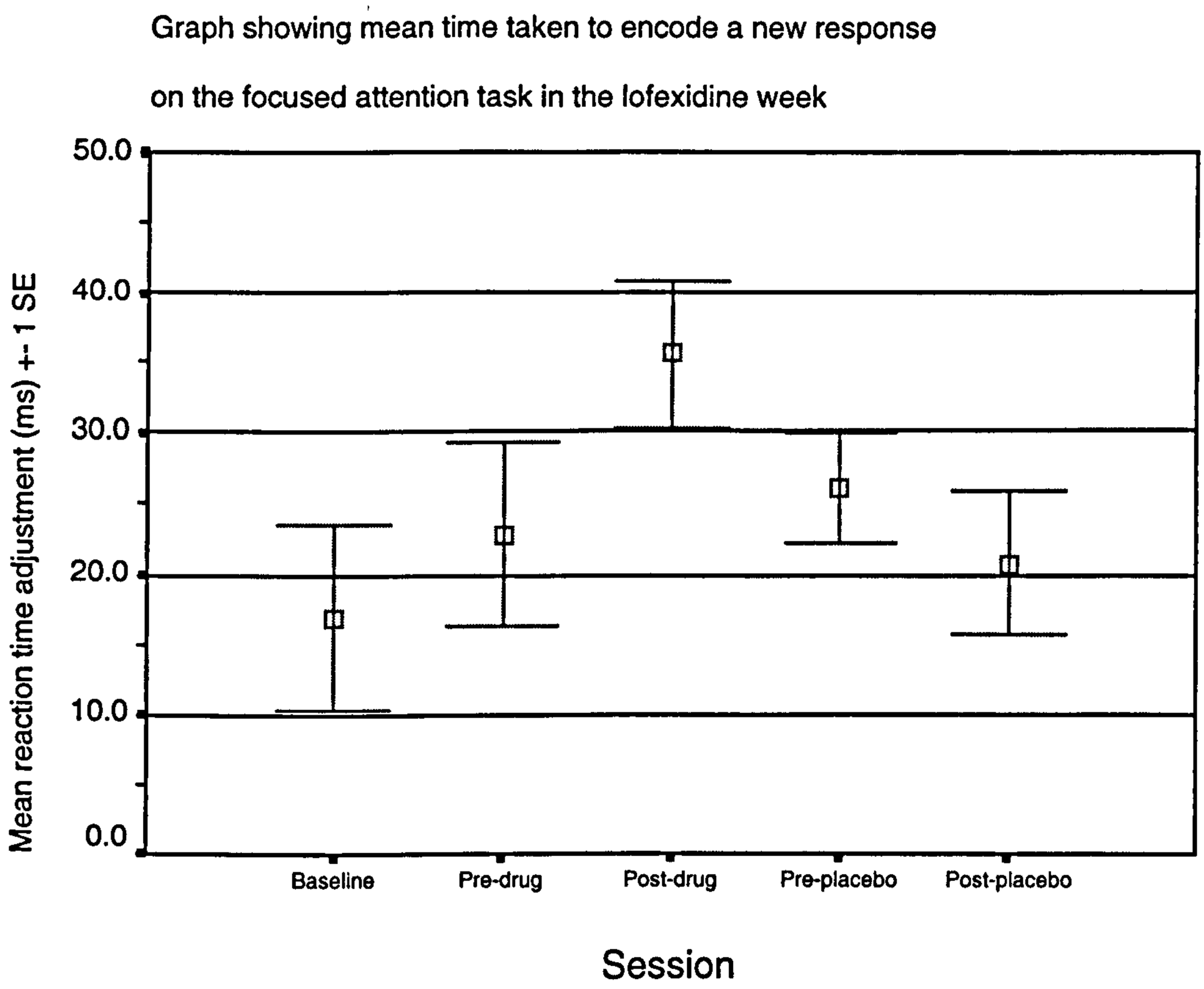


Figure 7.4 **Graph showing mean reaction time on trials in the categoric search task in the lofexidine week where target is repeated from previous trial**

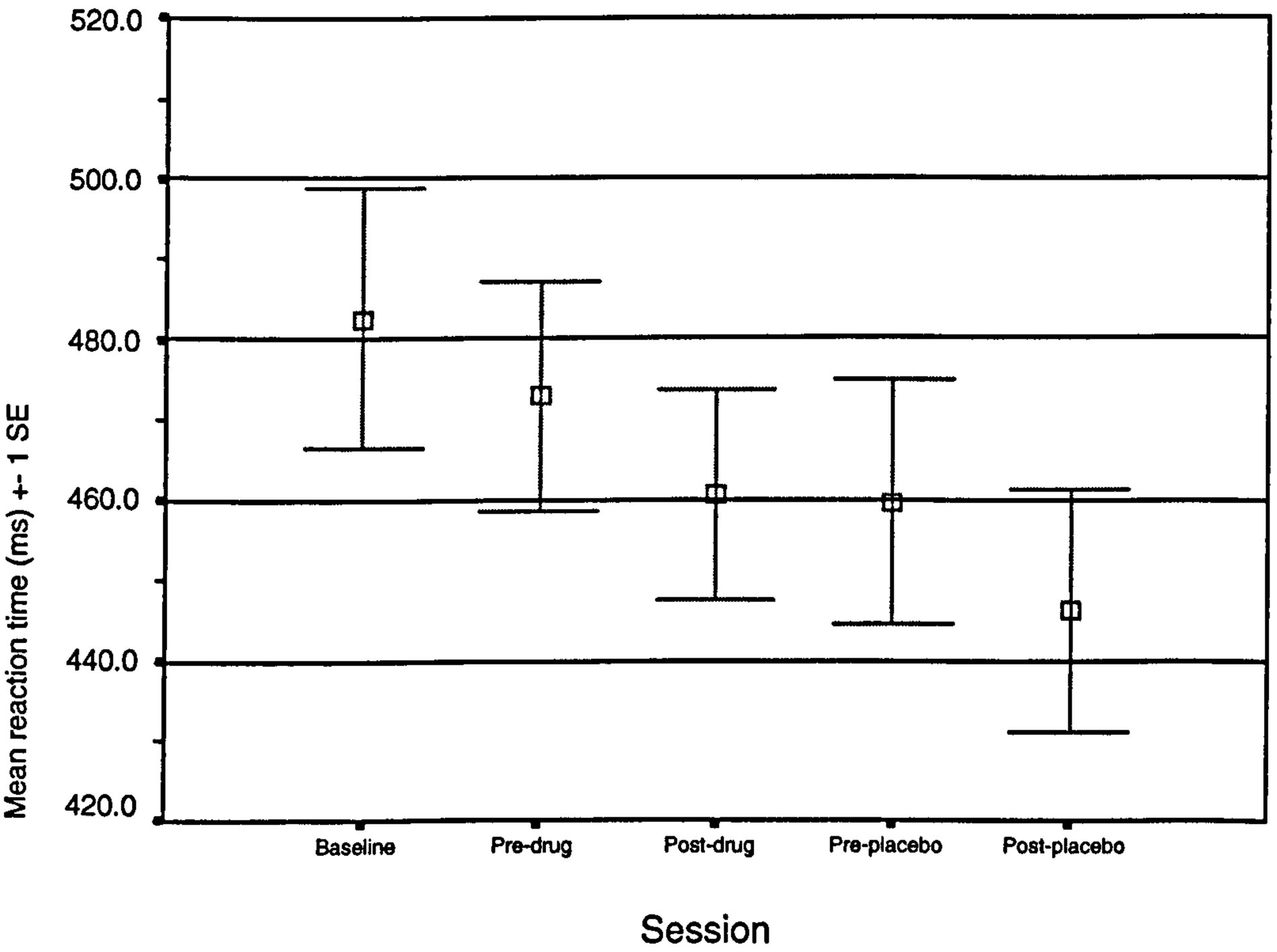


Figure 7.5 **Graph showing mean adjustment to reaction time caused by presentation of distracters in 'far' and 'compatible' conditions in categoric search task in the lofexidine week.**

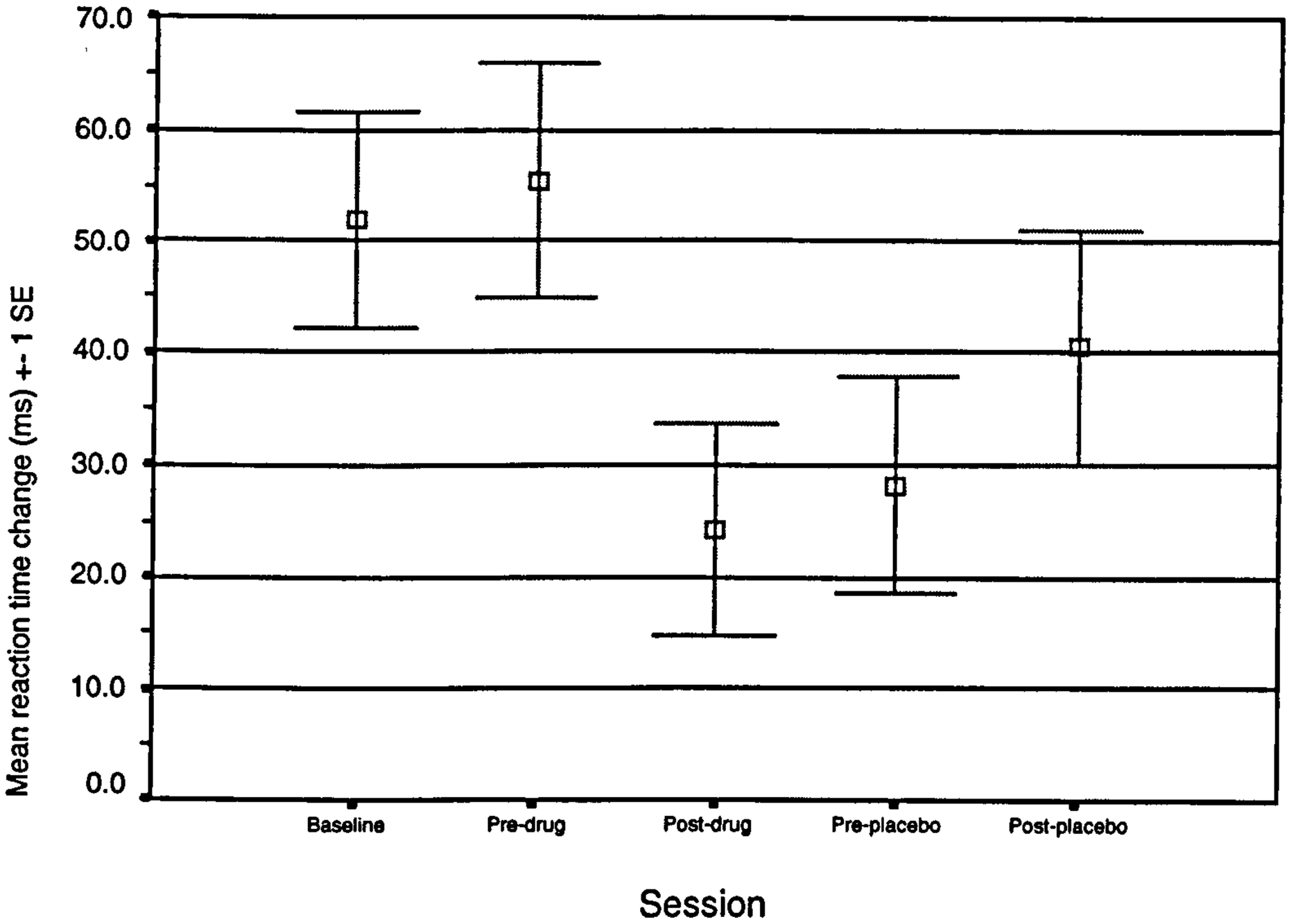


Figure 7.6 **Graph showing mean reaction time to trials where target is presented in the same location as the previous trial in categoric search task in the nicotine week.**

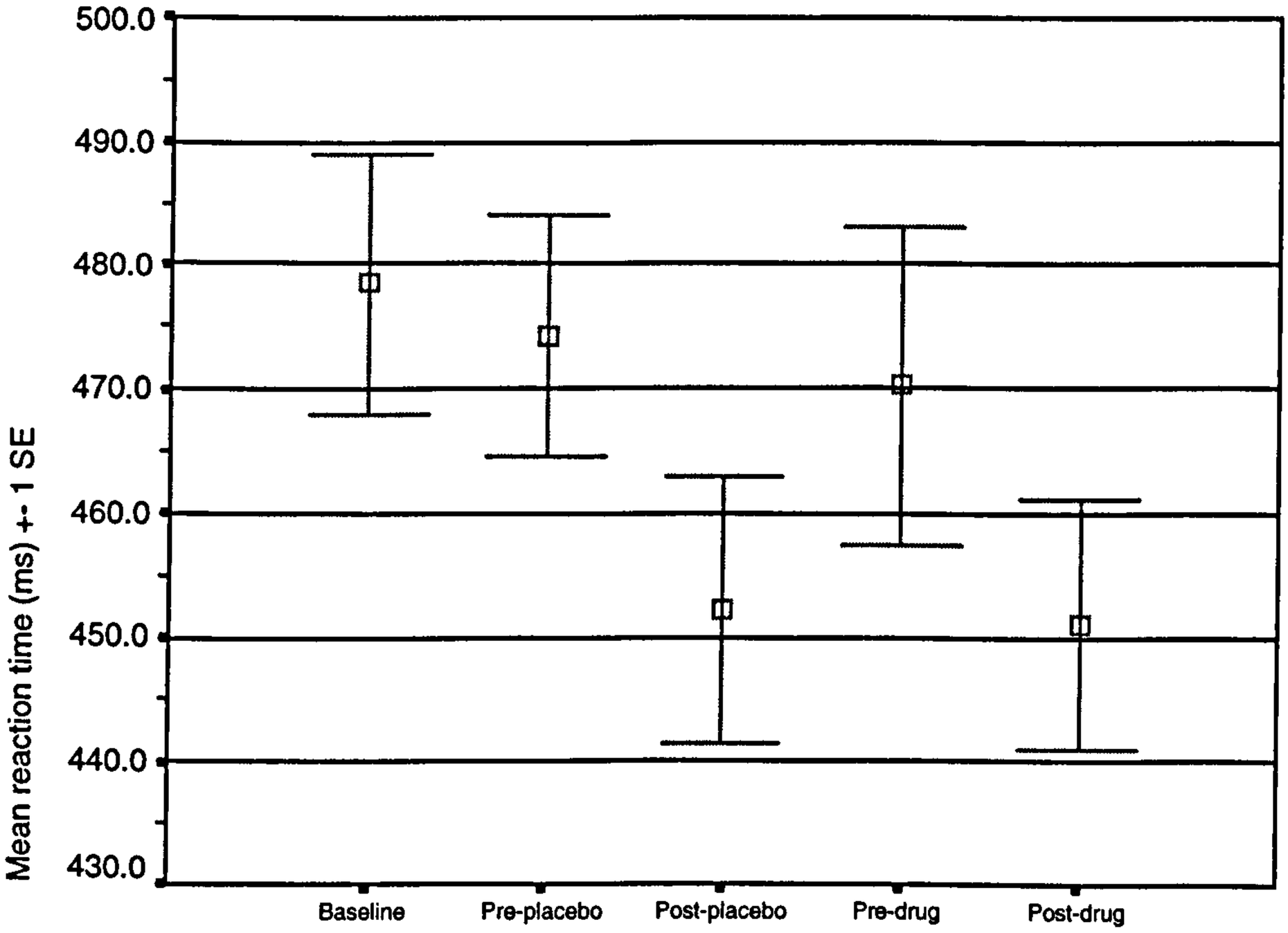


Figure 7.7 Graph showing mean total number of 'hits' on repeated digits RVIP task during the nicotine week.

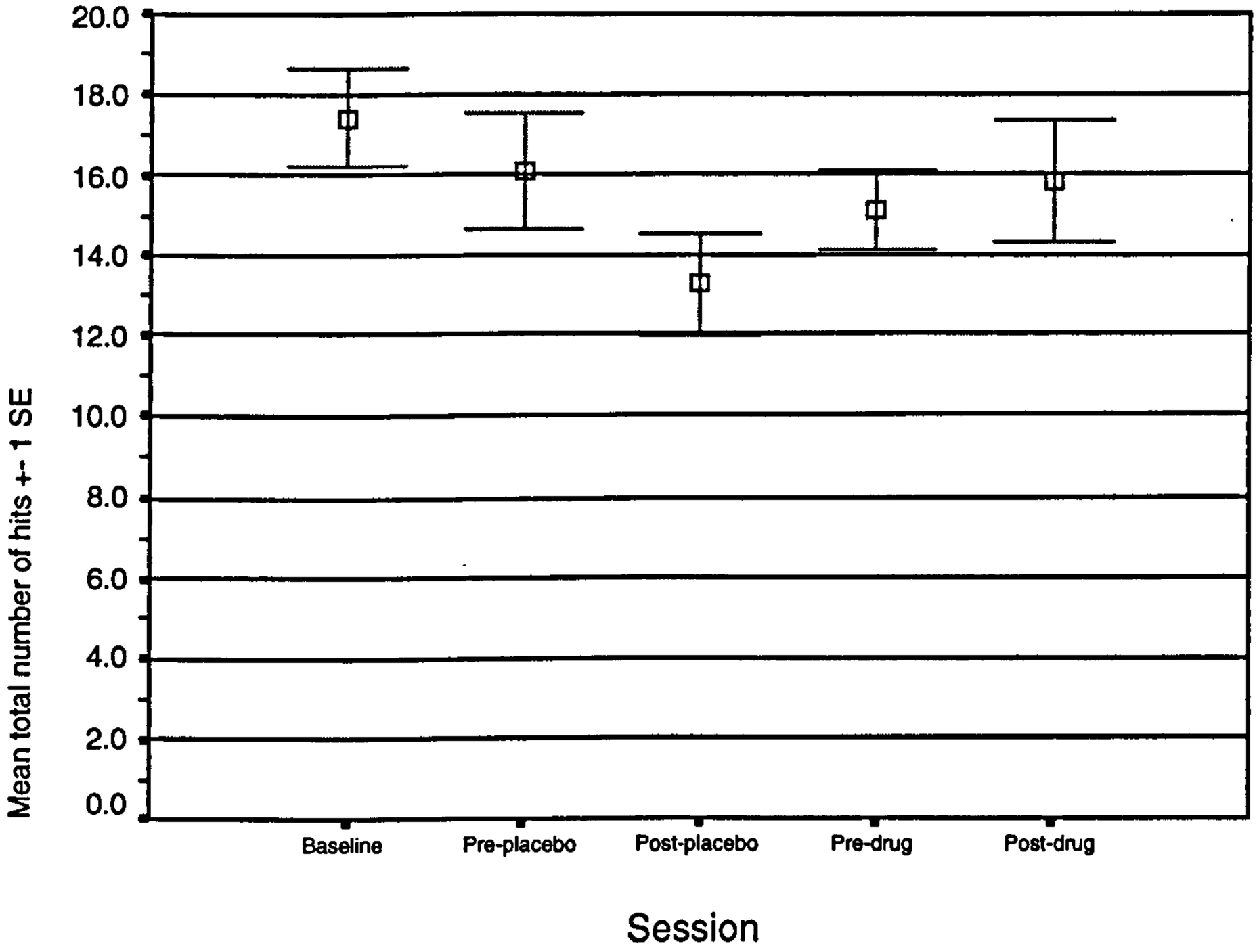


Figure 7.8 Graph showing mean pre-test alertness ratings (visual analogue) during sessions in the nicotine week.

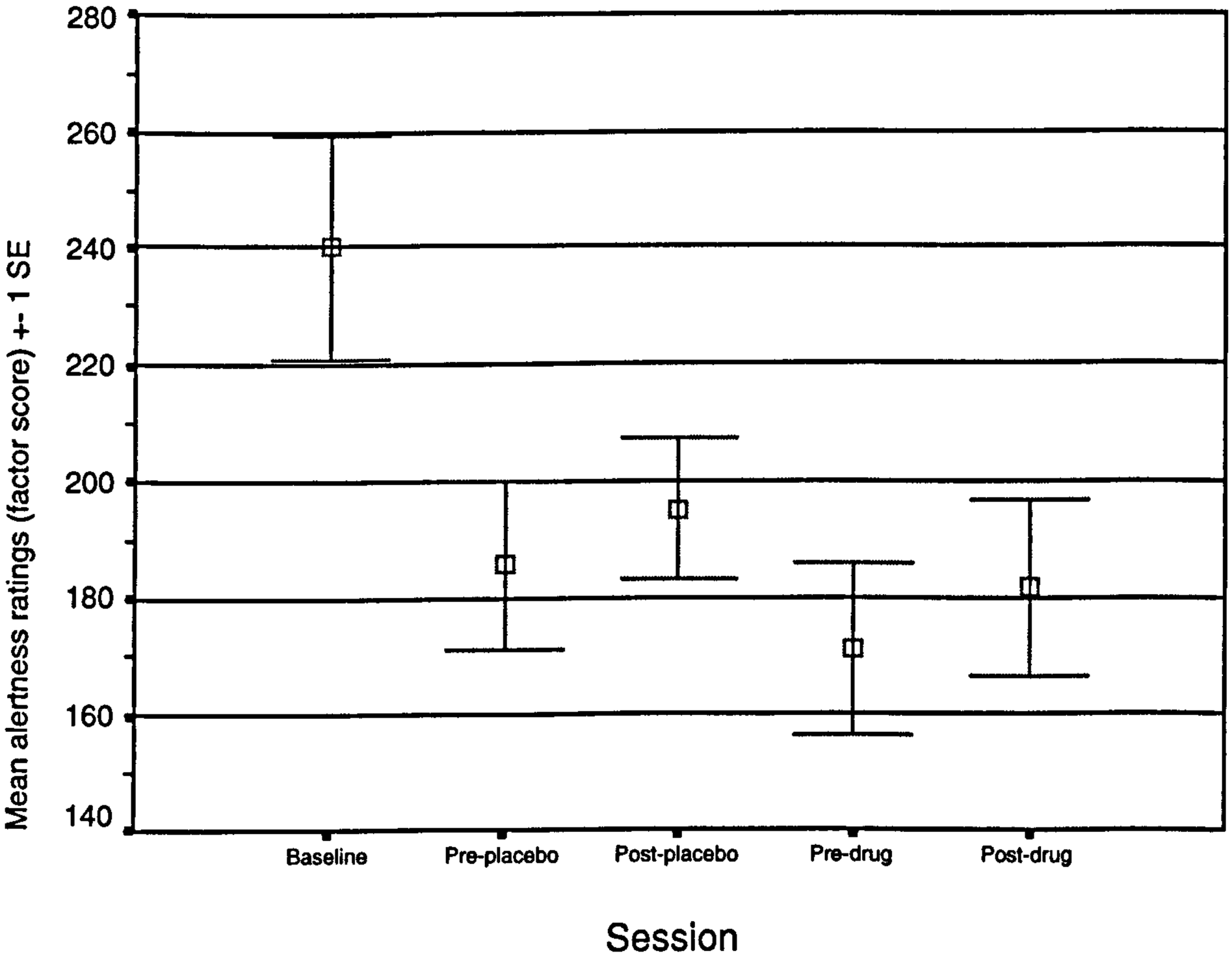


Figure 7.9 Graph showing mean post-test alertness ratings (visual analogue) during sessions in the nicotine week.

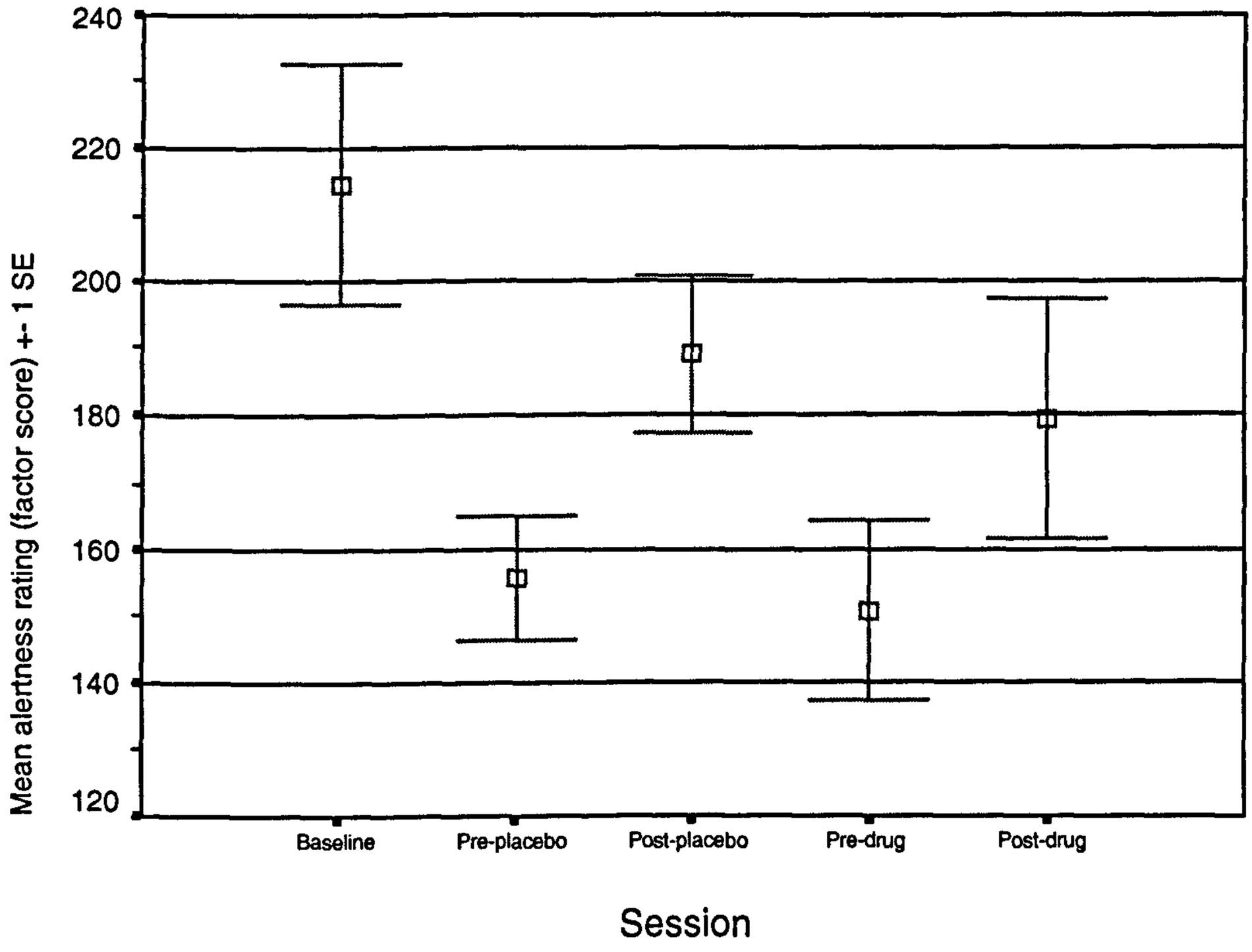


Figure 7.10 Graph showing mean pre-test hedonic tone ratings (visual analogue) during sessions in the nicotine week.

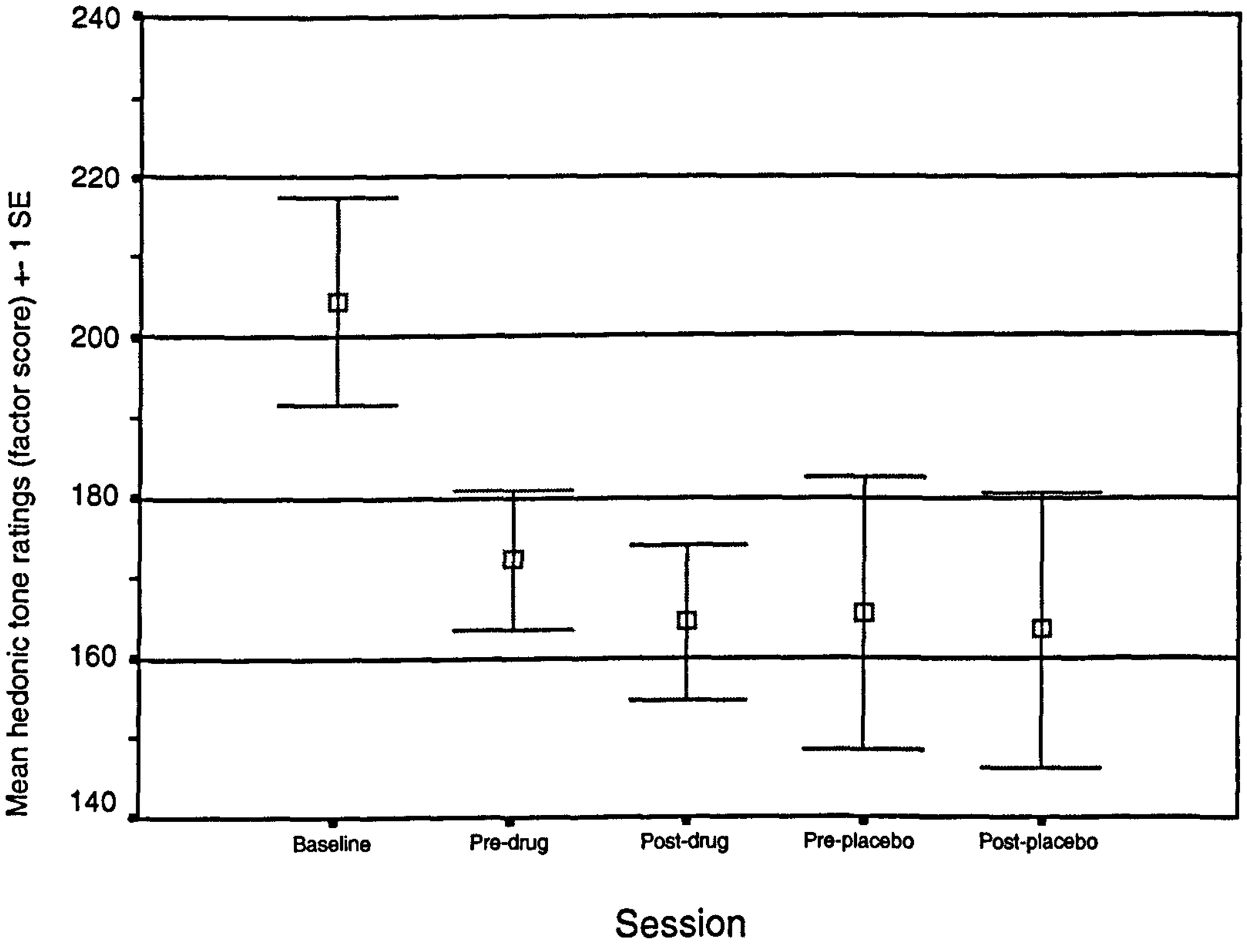


Figure 7.11 Graph showing mean post-test hedonic tone ratings (visual analogue) during sessions in the nicotine week.

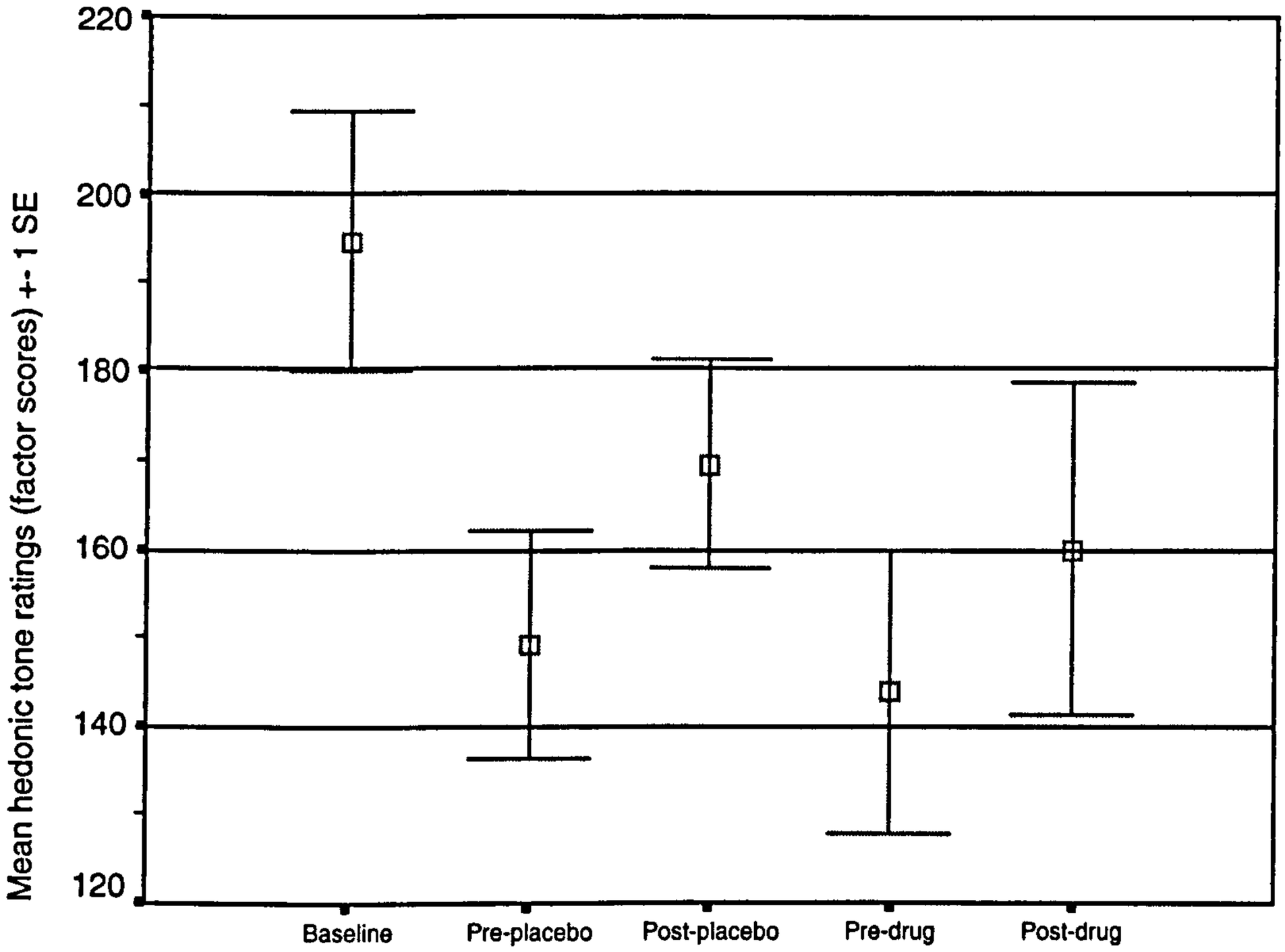


Figure 7.12 Graph showing mean post-test anxiety ratings (visual analogue) during sessions in the lofexidine week.

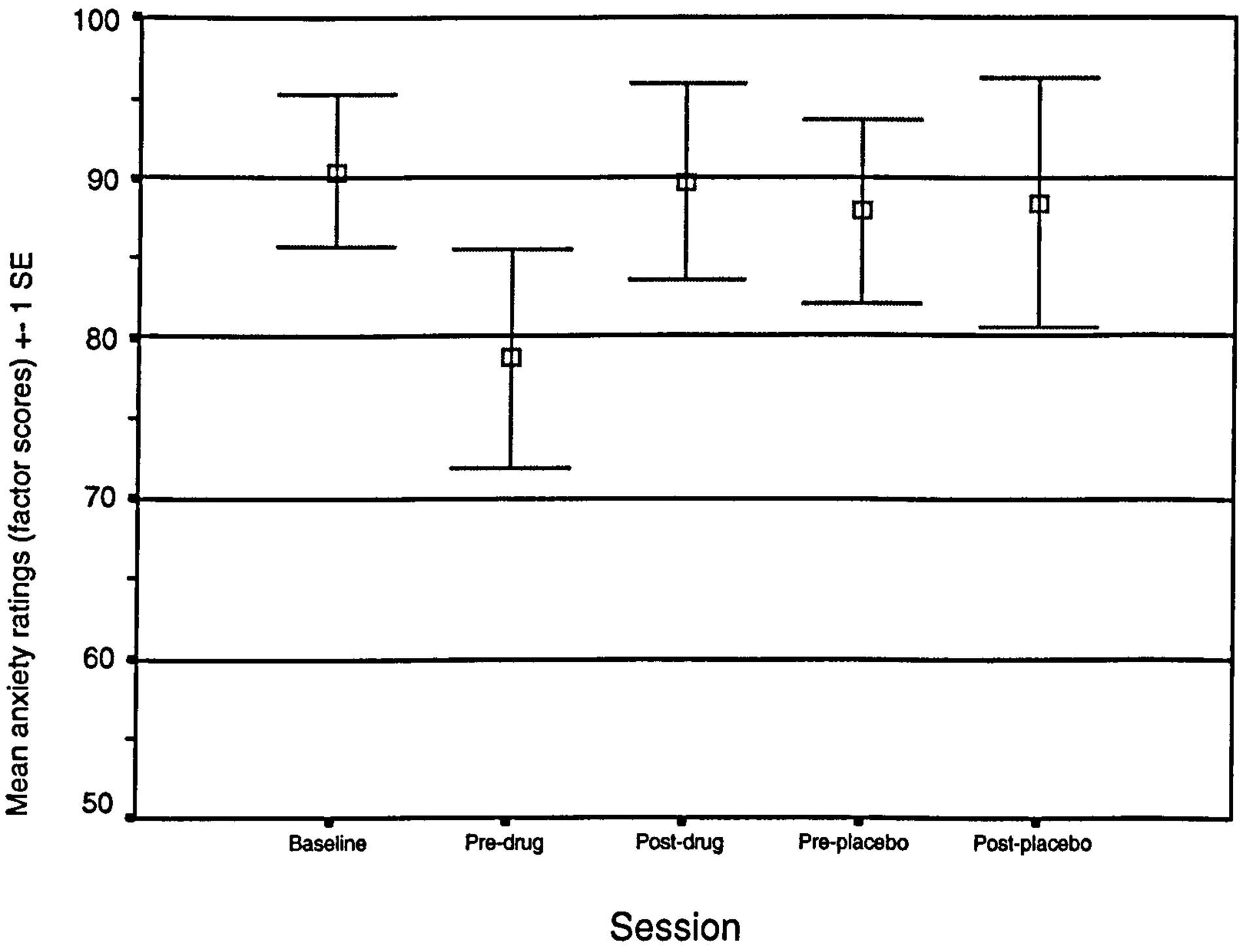


Figure 7.13

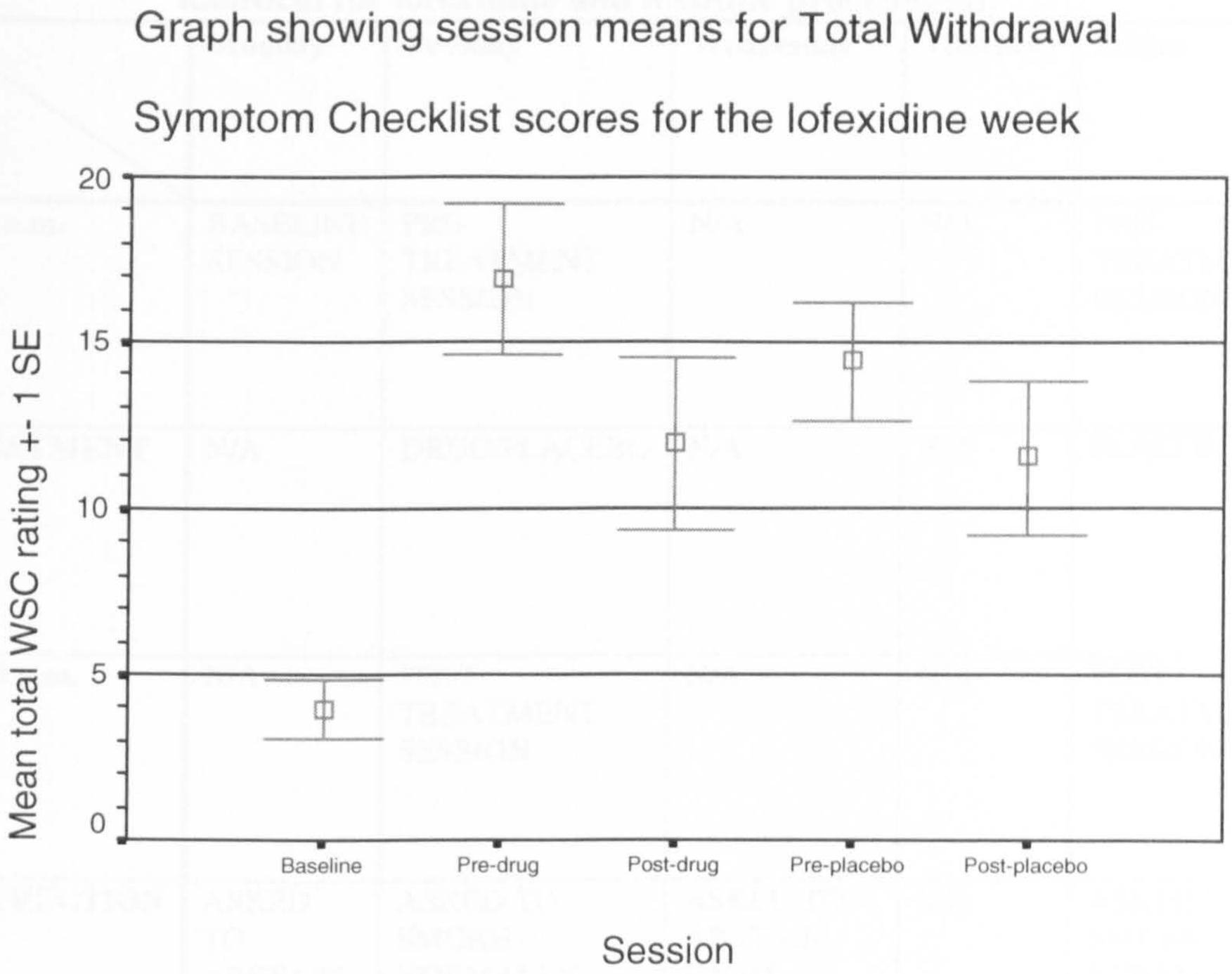


Figure 7.14 Graph showing mean total ratings in the nicotine and lofexidine study weeks on the WSC and OWS.

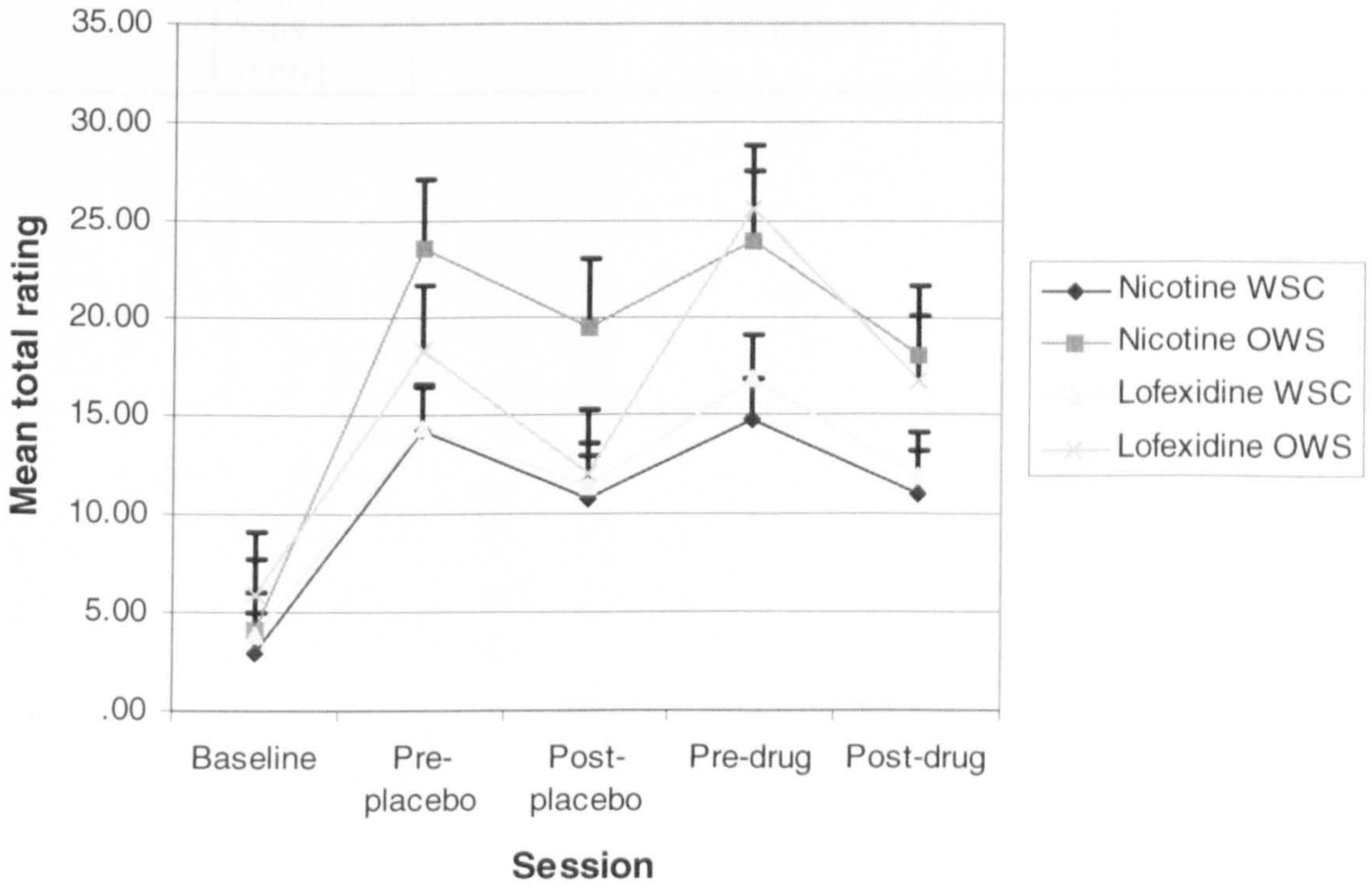


Table 7.1 Tabulated procedure for one experimental week (these were identical for lofexidine and nicotine procedures).

	Monday	Tuesday	Wednesday	Thursday	Friday
9.00 a.m.	BASELINE SESSION	PRE-TREATMENT SESSION	N/A	N/A	PRE-TREATMENT SESSION
TREATMENT	N/A	DRUG/PLACEBO	N/A	N/A	PLACEBO/DRUG
10.30 a.m.	N/A	POST-TREATMENT SESSION	N/A	N/A	POST-TREATMENT SESSION
INSTRUCTION	ASKED TO ABSTAIN FROM SMOKING FOR 24-HOURS FROM THIS POINT	ASKED TO SMOKE NORMALLY UNTIL FURTHER INSTRUCTION	ASKED TO ABSTAIN FROM SMOKING FOR 24-HOURS FROM FOLLOWING MORNING	N/A	ASKED TO SMOKE NORMALLY or DEBRIEFED

Table 7.2 **Summary of cognitive performance results; general effect on performance following 24-hour abstinence from smoking, lofexidine administration, nicotine administration, and both types of placebo. (↑ = improvement in performance compared to baseline, ↓ = deficit in performance compared to baseline; → = no significant change compared to baseline. Double arrows represents many variables affected).**

		WITHDRAWAL	NICOTINE	NIC.PLACEBO	LOFEXIDINE	LOFEX.PLACEBO
FOCUSED ATTENTION TASK	ACCURACY	↓↓	→	→	→	→
	REACTION TIME	→	↑	→	↓	→
CATEGORIC SEARCH TASK	ACCURACY	↓	→	→	↑	→
	REACTION TIME	↑	↑	↑↑	↑	↑
REPEATED DIGITS / RVIP TASK	ACCURACY	↓	→	↓	→	→
	REACTION TIME	↑	→	↑	→	→

Table 7.3 Mean accuracy of responses to targets presented alone or with asterisks on the focused attention task during the lofexidine week.

SESSION	Baseline	Pre-lofexidine	Post-lofexidine	Pre-placebo	Post-placebo
MEAN ACCURACY (STANDARD ERROR) number of correct responses	3.89 (0.02)	3.86 (0.03)	3.79 (0.05) •	3.85 (0.01) •	3.77 (0.03)*

Significance levels of differences to Baseline (without Bonferroni correction) * p<.001, • p<.05

Table 7.4 Mean accuracy of responses to targets alternating from previous trial on the focused attention task during the lofexidine week.

SESSION	Baseline	Pre-lofexidine	Post-lofexidine	Pre-placebo	Post-placebo
MEAN ACCURACY (STANDARD ERROR) number of correct responses	3.86 (0.03)	3.80 (0.04)	3.77 (0.05)	3.79 (0.03) •	3.70 (0.04)*

Significance levels of differences to Baseline (with Bonferroni correction) * p<.01, • p<.05

Table 7.5 Mean reaction time taken to encode a new response on the focused attention task, during the lofexidine week.

SESSION	Baseline	Pre-lofexidine	Post-lofexidine	Pre-placebo	Post-placebo
MEAN REACTION TIME (STANDARD ERROR) milliseconds	19.94 (6.57)	22.73 (6.50)*	35.58 (5.24)*	26.08 (3.87)	20.78 (5.06)

Significance levels of differences (without Bonferroni correction) * p<.005

Table 7.6 Mean reaction time on trials in categoric search task where target is repeated from previous trial, during the lofexidine week.

SESSION	Baseline	Pre-lofexidine	Post-lofexidine	Pre-placebo	Post-placebo
MEAN REACTION TIME (STANDARD ERROR) milliseconds	482.55 (16.13)	472.85 (14.24)	460.54• (13.18)	459.65• (15.17)	446.19* (15.15)

Significance levels of differences to Baseline (without Bonferroni correction) * p<.01, • p<.05

Table 7.7 Mean effect on reaction time of presenting a distracter in trials where the target is in the 'far' and 'compatible' condition in the categoric search task, during the lofexidine week.

SESSION	Baseline	Pre-lofexidine	Post-lofexidine	Pre-placebo	Post-placebo
MEAN REACTION TIME (STANDARD ERROR) milliseconds	51.84 (9.77)	55.33* (10.52)	24.17* (9.44)	28.18 (9.57)	40.54 (10.48)

Significance levels of differences (without Bonferroni correction) * p<.05

Table 7.8 Mean reaction time on trials where the target is presented in the same location as the previous trial in the categoric search task; nicotine week.

SESSION	Baseline	Pre-placebo	Post-placebo	Pre-nicotine	Post-nicotine
MEAN REACTION TIME (STANDARD ERROR) milliseconds	478.48 (10.45)	474.26 (9.77)	452.25 (10.72)	470.26* (12.86)	451.09* (10.11)

Significance levels of differences (without Bonferroni correction) * p<.05

Table 7.9 Mean total number of 'hits' made in the repeated digits vigilance task during the nicotine week.

SESSION	Baseline	Pre-placebo	Post-placebo	Pre-nicotine	Post-nicotine
MEAN TOTAL HITS (STANDARD ERROR) number of correct responses	17.42 (1.18)	16.08 (1.42)*	13.25 (1.26)*	15.08 (1.00)	15.83 (1.5)

Significance levels of differences (without Bonferroni correction) * p<.001

Table 7.10 Mean pre-test alertness ratings on the visual analogue mood scales during the nicotine week.

SESSION	Baseline	Pre-placebo	Post-placebo	Pre-nicotine	Post-nicotine
MEAN RATING (STANDARD ERROR) factor score	240.17 (19.15)	185.58* (14.54)	195.08 (12.10)	171.17• (14.50)	181.75 (15.20)

Significance levels of differences to baseline (without Bonferroni correction) * p<.01, • p<.025

Table 7.11 Mean post-test alertness ratings on the visual analogue mood scales during the nicotine week.

SESSION	Baseline	Pre-placebo	Post-placebo	Pre-nicotine	Post-nicotine
MEAN RATING (STANDARD ERROR) factor score	214.58 (18.07)	155.75 (9.46)	189.0 (11.9)	150.67* (13.50)	179.33* (17.88)

Significance levels of differences (without Bonferroni correction) * p<.025

Table 7.12 Mean pre-test hedonic tone ratings on the visual analogue mood scales during the lofexidine week.

SESSION	Baseline	Pre-lofexidine	Post-lofexidine	Pre-placebo	Post-placebo
MEAN RATING (STANDARD ERROR) factor score	204.42 (12.94)	172.25• (8.67)	164.42 (9.60)	165.50* (17.13)	163.42 (17.26)

Significance levels of differences to baseline (without Bonferroni correction) * p<.025, • p<.05

Table 7.13 Mean post-test hedonic tone ratings on the visual analogue mood scales during the nicotine week.

SESSION	Baseline	Pre-placebo	Post-placebo	Pre-nicotine	Post-nicotine
MEAN RATING (STANDARD ERROR) factor score	194.50 (14.75)	149.17* (12.96)	169.50* (11.76)	143.92 (16.07)	159.83 (18.64)

Significance levels of differences (without Bonferroni correction) * p<.01

Table 7.14 Mean post-test anxiety ratings on the visual analogue mood scales during the lofexidine week (HIGHER score represents LOWER anxiety).

SESSION	Baseline	Pre-lofexidine	Post-lofexidine	Pre-placebo	Post-placebo
MEAN RATING (STANDARD ERROR) factor score	90.42 (4.85)	78.75 (6.78)	89.75 (6.22)	87.83 (5.86)	88.33 (7.86)

Table 7.15 Mean (Standard error) WSC/OWS total scores for all conditions in lofexidine and nicotine weeks.

	Baseline	Pre-placebo	Post-placebo	Pre-drug	Post-drug
NICOTINE	6.67 (2.03)	38.0 (7.02)	30.0 (8.03)	38.92 (8.23)	28.75 (7.48)
LOFEXIDINE	9.58 (1.84)	33.08 (4.57)	21.92 (4.64)	43.33 (7.63)	28.08 (7.14)

Table 7.16 Spearman's Rho correlation coefficients between WSC and OWS for each session during the two experimental weeks.

	Baseline	Pre-placebo	Post-placebo	Pre-drug	Post-drug
NICOTINE	r=0.238	r=0.646•	r=0.724**	r=0.868*	r=0.395
LOFEXIDINE	r=0.576•	r=0.711**	r=0.458	r=0.483	r=0.744**

*p<.001, **p<.01, •p<.05 – all 1-tailed significance levels

Table 7.17 Means (std. error) of QSU Factor 1 scores in all sessions.

	Baseline	Pre-placebo	Post-placebo	Pre-drug	Post-drug
NICOTINE	-18.5 (4.4)	10.1 (3.2)	5.9 (3.5)	9.8 (2.7)	5.5 (3.8)
LOFEXIDINE	-16.3 (3.2)	10.0 (3.1)	0.0 (4.7)	12.1 (2.2)*	7.3 (3.0)*

* - means differ significantly p<.05

Table 7.18 Means (std. error) of QSU Factor 2 scores in all sessions.

	Baseline	Pre-placebo	Post-placebo	Pre-drug	Post-drug
NICOTINE	27.2 (3.1)	49.3 (3.7)	46.7 (4.4)	51.3 (3.9)	48.6 (4.2)
LOFEXIDINE	31.1 (2.5)	48.8 (4.3)	43.4 (4.8)	52.8 (4.1)	48.5 (4.5)

Table 7.19 Mean (std. error) POMS 'Tension' factor scores in all sessions.

	Baseline	Pre-placebo	Post-placebo	Pre-drug	Post-drug
NICOTINE	3.9 (0.8)	12.9 (2.9)	9.2 (2.9)	10.2 (2.3)	8.8 (2.7)
LOFEXIDINE	5.0 (1.1)	8.3 (1.6)	5.4 (1.3)	11.1 (2.0)*	8.0 (2.2)*

* - means differ significantly p<.05

Table 7.20 Mean (std. error) POMS 'Vigour' factor scores in all sessions.

	Baseline	Pre-placebo	Post-placebo	Pre-drug	Post-drug
NICOTINE	10.7 (1.4)	6.5 (2.2)	5.6 (1.5)	5.6 (1.1)	6.1 (1.4)
LOFEXIDINE	10.9 (1.9)	8.8 (1.5)	6.6 (1.2)	7.8 (1.5)*	4.7 (1.4)*

* - means differ significantly p<.05

Table 7.21 Mean (std. error) POMS 'Confusion' factor scores in all sessions.

	Baseline	Pre-placebo	Post-placebo	Pre-drug	Post-drug
NICOTINE	3.8 (0.8)	8.0 (1.4)	7.2 (1.6)	6.8 (1.5)	6.3 (1.2)
LOFEXIDINE	5.2 (0.9)	6.5 (1.2)	6.6 (1.2)	7.4 (1.4)	7.9 (1.7)

Chapter 8 – Discussion

8.1 Synopsis of major findings

The primary aim of this research was to generate a multi-disciplinary picture of tobacco dependence, with a particular focus on the associated withdrawal syndrome. This is important since tobacco smoking is a highly complex addictive behaviour comprising a variety of social and biological components. Using psychological, psychopharmacological, psychosocial and genetic data different subtypes of smoker were characterised, and their responses to withdrawal and reinstatement were investigated. Finally, the involvement of noradrenergic activity on tobacco withdrawal was examined.

Addicted and non-addicted smoker subgroups were profiled by creating a composite Addiction Index score. This was achieved by combining nicotine tolerance data and dependence-related smoking motivation data. It was believed that measuring the combined motivation and tolerance aspects of smoking would provide a more effective characterisation of tobacco addiction than either measure would individually. This reflects both the physical and psychological dependence attributes of nicotine addiction. The observed association between Addiction Index scores and the latency to first cigarette of the day effectively demonstrated this.

How soon people smoke their first cigarette after waking is considered a measure of dependence, with those who smoke very soon after waking theoretically demonstrating high nicotine tolerance. Although all addicted smokers had their first cigarette in the first hour of the day, several non-addicted smokers also reported this

pattern of behaviour. This finding demonstrates the nature of the problem in addiction research, particularly with smoking; what are the defining features? What psychopharmacological phenomena best discriminate between addicted and non-addicted smokers? Clearly tolerance is important, but cannot perfectly describe the behavioural and motivational aspects of smoking. Therefore, the two groups might be different in other ways. What happens to smokers following abstinence is of particular interest, due to the tobacco withdrawal syndrome.

Since smokers often report using tobacco to help them either relax or concentrate, addicted and non-addicted smokers' changes in mood and cognitive performance following withdrawal and subsequent reinstatement was examined. Twenty-four hour withdrawal caused increases in anxiety in the addicted but not non-addicted smokers. An unpredicted finding was that addicted smokers cognitive performance was improved on several tasks following withdrawal. Reinstatement improved all smokers' alertness and hedonic tone, whilst the addicted group derived some reduction in anxiety. The non-addicted smokers performance on a categoric search task was improved by reinstatement.

These results could be interpreted as demonstrating that non-addicted smokers may be deriving more attentional benefits from smoking, whereas addicted smokers might be modulating levels of anxiety. Whether the anxiety fluctuations experienced by addicted smokers in tobacco withdrawal and reinstatement were simply caused by withdrawal and removed by reinstatement, or were related to independent levels of trait anxiety was not clear. If these findings are concretely related to withdrawal sensitivity, addicted smokers may display neurobiological differences to non-addicted

smokers. The different mood and performance effects derived by the two groups may reflect differences in nAChR distribution or activity, or differences in dopaminergic reward systems.

Potential differences in dopamine receptor morphology were examined. Since previous work has shown genetic differences in DRD2, DRD3 and DRD4 between drug users and non-users (in some cases specifically with nicotine), genetic polymorphisms of these receptors were examined. D2 and D3 polymorphisms were not shown to differ significantly between addicted and non-addicted smokers. However, a greater proportion of addicted smokers possessed the D4 L allele than non-addicted smokers.

Furthermore, the D4 L allele was associated with the Novelty Seeking personality trait, and particularly the Impulsiveness subscale of this trait. The results suggest that DRD4 polymorphisms may impact on nicotine dependence, although perhaps via associated personality variables rather than through different neurobiological reward or reinforcement systems. Since psychological factors such as anxiety and impulsiveness were emerging as powerful discriminatory parameters between the addicted and non-addicted smokers, a more wide-ranging psychosocial contrast between the groups was performed.

All smokers reported greater perceived stress and more cognitive failures (absent-mindedness) than non-smokers. It is difficult to conclude whether this reflects the multiple episodes of tobacco withdrawal and reinstatement throughout the day, or is a true representation of baseline differences between the groups. Smokers may even

potentially be attempting to self-medicate these difficulties and were it not for nicotine use the differences may be even more marked.

Unsurprisingly, smokers had different health orientations to non-smokers; greater anxiety about health, lower health confidence and reasons to be healthy. Addicted smokers reported more anxious and depressive symptoms than non-addicted smokers. Again, this is difficult to interpret, since it may reflect either anxiety or dysphoria associated with episodes of acute tobacco withdrawal for the addicted smokers, or represent true baseline differences between the groups. The severity of tobacco withdrawal syndrome could possibly account for some of the major differences emerging thus far in the research. Therefore, differences between addicted and non-addicted smokers craving and symptomatological responses to abstinence and reinstatement were profiled.

Twenty-four hour abstinence was shown to increase ratings of withdrawal symptoms in all smokers. Addicted smokers experienced greater increases in craving for tobacco, restlessness and sleep disturbance than non-addicted smokers. It is plausible that these three symptoms could be linearly related. Increased craving for tobacco not treated by smoking may lead directly to restlessness, either through psychopharmacological withdrawal or through suspension of stereotypical psychomotor routines. This restlessness could then persist after the individual has gone to bed leading to disturbed sleep, most likely characterised by increased sleep latency.

Although all urges to smoke measured by the Questionnaire of Smoking Urges (Tiffany & Drobes, 1991) were rated higher in withdrawal by all smokers, non-addicted smokers reported greater increases in urges pertaining to positive reinforcement whereas addicted smokers urges to smoke relating to negative reinforcement were significantly increased. This can be summarised as addicted smokers experiencing a more severe withdrawal syndrome than non-addicted smokers, and the subsequent urges to smoke were essentially based on removing or ameliorating those withdrawal symptoms.

Notably, increases in anxiety following withdrawal were not significantly different between addicted and non-addicted smokers. This contrasts with mood findings earlier in the thesis showing anxiety selectively significantly increasing in addicted smokers following abstinence. This may reflect the different methodologies, as the "Anxiety" mood measure discussed in Chapter 3 was a factorised construct amalgamating several bi-polar visual analogue scales, whereas the "Anxiety" symptomatology measure in Chapter 6 was a singular uni-polar item measured by Likert-scale. Alternatively, the temporal proximity of the mood ratings in Chapter 3 to the cognitive performance tests may have confounded results. If subjects were concerned about their performance on the tasks (either before or after the battery), this may have interacted with the greater severity of withdrawal state in the addicted smokers to produce the observed increases in anxiety ratings.

Nicotine reinstatement through *ad libitum* smoking reduced all those urges to smoke and ratings of withdrawal symptoms intensified by abstinence. This is consistent with previous work in most drugs of abuse with a withdrawal syndrome, in that

reinstatement of that drug rapidly ameliorates the perceived negative symptoms of withdrawal. Addicted smokers derived greater relief from craving for tobacco than non-addicted smokers, although this was because addicted smokers had higher craving ratings in the withdrawn session.

Lofexidine, an α2-adrenoceptor agonist used successfully to treat opiate withdrawal was compared to NRT in terms of effects on impairments in mood and cognitive performance associated with the tobacco withdrawal syndrome. The cognitive tasks selected were those demonstrating significant withdrawal effects in Chapter 3. Although few of the observed effects survived Bonferroni correction, nicotine and lofexidine were shown to alleviate some deficits associated with withdrawal, but each drug affected different mood and performance variables. This may suggest that different withdrawal symptoms are mediated by different neurotransmitters. Some problems may be a result of decreased cholinergic function, and these may be directly alleviated by nicotine, whereas others may be a result of increased noradrenergic activity, and thus mitigated by lofexidine.

Addicted smokers experienced decreased accuracy but also decreased reaction times on several performance tasks following tobacco withdrawal. These effects were ascribed either to direct psychopharmacological effects of withdrawal or to reflect subjects' performing tasks faster and less accurately in order to smoke sooner. Accuracy and reaction time variables on the categoric search task were improved by lofexidine, but had no positive effect on cognitive performance in other tasks. Nicotine inhalator was shown to improve reaction times on the focused attention and categoric search tasks. In contrast with previous research, there was no nicotine effect

on RVIP performance. Ratings of alertness and hedonic tone were lower in tobacco withdrawal compared to non-deprived. These ratings were increased by nicotine, but not by lofexidine.

Ratings of severity of withdrawal symptoms measured by tobacco and opiate withdrawal checklists were increased following 24-hour abstinence. Many of the items on the two questionnaires were similar, suggesting that there are common components of withdrawal syndromes for several drugs of abuse. Ratings of urges to smoke were also increased by withdrawal, consistent with findings in Chapter 6. Withdrawal lead to increased ratings on confusion and tension factors, and reduced vigour. These are consistent with more specific symptoms of the withdrawal syndrome, particularly difficulty concentrating, anxiety, irritability and restlessness, and drowsiness. After lofexidine was administered, subjects rated the overall severity of their withdrawal symptoms lower, rated urges to smoke pertaining to positive reinforcement lower, and rated tension and vigour lower. The latter demonstrated the predicted anxiolytic and sedative effects of lofexidine.

Nicotine inhalator was also shown to reduce severity ratings of withdrawal symptoms on the checklists, but interestingly did not reduce ratings of urges to smoke. Nicotine also had no effect on the impaired mood factors. These lack of effects were ascribed to the very low dose of nicotine delivered by this procedure. It was calculated *post hoc* that the nicotine delivered by eight puffs on an inhalator equates to half a puff on a cigarette. This may have been simply insufficient to effectively ameliorate the tobacco withdrawal syndrome.

Lofexidine showed some interesting effects on the tobacco withdrawal syndrome, and might require further investigation. If the sedative effects of the drug could be mitigated, the drug may have some anxiolytic benefit in ameliorating nicotine withdrawal. Lofexidine could potentially be used adjunctively with NRT to broaden the psychopharmacological management of symptoms associated with smoking cessation.

The implications of the positive effects of lofexidine on tobacco withdrawal should also be investigated. Noradrenergic involvement in opiate withdrawal is well documented, but little human work has been performed in relation to tobacco withdrawal. The noradrenergic action of bupropion may be one important mechanism of the drug's efficacy in promoting smoking cessation. There may be scope for examining neurobiological differences in noradrenergic structures, such as distribution of receptor subtypes, relative densities or affinities of receptors.

8.2 Addicted and non-addicted smokers

One of the major achievements of this research was to create a composite score for tobacco dependence taking both physical (tolerance) and psychological (motivational) factors into account. Following some post-hoc refinement of the computational model, the Addiction Index score created allowed the sample of smokers to be characterised as either addicted or non-addicted, as evidenced by a modest bi-modal distribution of these scores.

The ability to divide a continuous variable into two functional groups in this way suggests that although there may be a continuum for levels of tobacco dependence,

smokers are effectively either addicted, or not. There was evidence for this throughout the thesis as evidenced by a variety of predicted differences between the groups.

The Addiction Index represents one way of characterising levels of nicotine dependence rather than a definitive figure. It is relatively resistant to self-report bias. By example, although all smokers in the addicted group claimed to be addicted to smoking, there were several smokers in the non-addicted group who also claimed to be addicted to smoking. Furthermore, the weighting of the components of the Addiction Index meant that tolerance scores did not overbear motivational scores, or vice versa. For example, although all the smokers in the addicted group consumed their first cigarette within an hour of waking, indicating high levels of tolerance, many non-addicted smokers also had short latencies to their first cigarette of the day.

An individual's levels of tobacco dependence are likely to fluctuate over time to some degree. The Addiction Index score provides a snapshot of dependence at a given moment, and could possibly be clinically useful to assess reductions in addiction perhaps in a phase of cutting down prior to cessation, or in terms of choosing the most effective NRT product.

Due to this likely temporal sensitivity, the non-addicted smokers group may have included individuals who were progressing towards addiction to smoking. These individuals may have had smoking histories that were too short, or been too constrained by situational factors (e.g. living with parents) to develop full-blown nicotine dependence. This point is of particular relevance where genetic factors were investigated (Chapter 4). Neurobiological differences predicted to be associated with

tobacco addiction might be in evidence, but since the non-addicted smokers group was so heterogeneous the relationship is not confirmed. Although a powerful tool, the Addiction Index score system should also take smoking history into account.

The terminology of convenience and temporal sensitivity associated with groupings derived using the Addiction Index score means that chippers (Shiffman, 1979; 1989), a group demonstrating stable longstanding non-dependence may feature differences lost in the grouping methodology. Although certain differences found between addicted and non-addicted smokers might be valid, they could be different to contrasts between chippers and regular smokers.

8.3 Craving, positive and negative reinforcement

Both addicted and non-addicted smokers experienced increased cravings for tobacco and urges to smoke following periods of 24-hour abstinence. However, the formulations of these urges were different according to the groups. Non-addicted smokers cited increased urges pertaining to the positive reinforcement aspects of smoking following withdrawal, whereas addicted smokers reported increased urges pertaining to the negative reinforcement aspects of smoking.

This exemplifies the importance of withdrawal symptomatology to the tobacco dependence phenomenon. Although all tobacco users will crave the positive reinforcement effects of nicotine (e.g. increased alertness), those exhibiting high levels of dependence will crave the negative reinforcing effects such as reduction of negative affect (see Chapter 6). This is explained by understanding that once tobacco dependence has developed fully, the mitigation of withdrawal symptoms caused by

periods of abstinence supersedes other factors to become perhaps the principal motivating factor driving smoking behaviour. Furthermore, it was found that with increased nicotine tolerance comes a depleted sensitivity to the positive reinforcing aspects of smoking, reducing the salience of these factors still further.

Interestingly, when 24-hour withdrawn addicted smokers were administered lofexidine, only urges to smoke pertaining to positive reinforcement were significantly reduced. Since lofexidine is commonly used to mitigate withdrawal symptoms in opiate detoxification (Strang, Bearn & Gossop, 1999) it was predicted that if any smoking urges were to be affected, those relating to negative reinforcement (broadly pertaining to withdrawal) would be moderated by the drug. This finding is made harder to explain by the concurrent result that lofexidine generally reduced severity of withdrawal symptoms, including craving for tobacco. Potentially, although lofexidine reduced some of the effects of tobacco withdrawal, subjects believed these effects could be reduced still further through smoking cigarettes.

It can be hypothesised that the positive reinforcement effects of nicotine are important at the initiation phase of smoking behaviour, but the negative reinforcement effects are critical in the persistence of smoking behaviour. This theory still leaves the problem of explaining the behavioural patterns of chippers, who are able to smoke a number of cigarettes each day over a long period of time, without becoming dependent on tobacco. It could be explained simply by their smoking far fewer cigarettes, thus lower nicotine intake, resulting in persistently low levels of tolerance.

However, this only shifts the question. How are chippers able to moderate their cigarette use rather than escalate to the levels most dependent smokers reach? The best explanation for this is to view chippers in terms of Shiffman's (1991) sensitivity model of smoking behaviour. Chippers could have a low initial sensitivity to nicotine, therefore deriving relatively lower levels of positive reinforcement from early episodes of smoking. Rather than becoming non-smokers, other factors possibly social in nature result in the characteristic pattern of long-term low-level smoking. Steady escalation of number of cigarettes smoked daily is characteristic of development of tobacco dependence. The putative reduced positive reinforcement during these early episodes could explain the blunted incremental increases in intake observed with chippers.

8.4 Cognitive performance and tobacco dependence

The existence of absolute effects of nicotine on cognitive performance is still a highly contentious issue (Heishman, 1998). What is clearer is the existence of impairments in cognition associated with the tobacco withdrawal syndrome (Hatsukami et al. 1985; Snyder et al. 1989). The precise mechanism by which tobacco withdrawal generates these effects is still unknown, although the relative reduction in frontal ACh activity and withdrawal-induced mood problems are likely candidates.

Findings in Chapter 3 were mixed in terms of consistency with previous research examining tobacco withdrawal and cognitive performance. Few clear differences were observed between addicted and non-addicted smokers, although the addicted group showed a general speeding up of reaction times from non-deprived to withdrawn sessions. These findings were interpreted as demonstrating a change, conscious or otherwise, in "response style" on the tasks; i.e. addicted subjects were responding as

quickly as possible in order to begin their period of *ad libitum* smoking as soon as possible.

Similarly, in Chapter 7 addicted smokers' reaction times often improved from baseline (non-deprived) to withdrawn sessions. Again this was interpreted as demonstrating a change in response style potentially motivated or encouraged by the knowledge that smoking could recommence once the test session had been completed.

The presence in both Chapters 3 and 7 of an imminent period where smoking would be allowed could be critical when contrasting current findings with those of Snyder et al. (1989). In general, withdrawal effects on cognitive performance in this thesis demonstrated improvements in reaction time and impairments in accuracy over a variety of tasks. Snyder et al. (1989) broadly found impairments in reaction times and little effect on accuracy in a comparable array of tasks. Importantly, Snyder et al.'s (1989) subjects were tested at regular intervals over a two-week period of abstinence. In other words, the rate of their task performance would have no impact on how soon they would be able to smoke. This contrasts with current research, whereby smokers may have believed that the sooner they completed the task batteries the sooner they would be able to resume smoking. This methodological difference may go some way toward explaining the difference between current findings and those of Snyder et al. (1989).

If faster reaction times were merely a by-product of utilising a particular response style with the aim of smoking as soon as possible, it would be predicted that following nicotine reinstatement reaction times would become slower. In Chapter 3, *ad libitum*

smoking was shown to increase reaction times in addicted smokers, but also in non-addicted smokers. Furthermore, these longer reaction times observed in the smoking groups were less increased than in the non-smokers group. The non-smokers would not have been changing their response style in order to reduce smoking latency, hence the interpretation that smoking "protected" both groups of smokers from boredom or fatigue effects in the reinstatement session.

The putative effects of tobacco deprivation on cognitive performance cannot be categorically ascribed to any one particular phenomenon on the strength of studies conducted as part of this thesis. However, it is possible that the accelerated reaction times observed in addicted smokers following withdrawal were due to changes in response style, perhaps driven by craving for tobacco.

8.5 Mood and arousal in nicotine withdrawal

The tobacco withdrawal syndrome described in DSM-IV includes important negative changes in mood and arousal. Symptoms such as irritability, restlessness and drowsiness are common following deprivation (Hughes & Hatsukami, 1986). A variety of instruments were used at various points in this thesis to examine the impact of withdrawal on mood and arousal. These included computer-administered visual analogue scales, and questionnaires such as Profile of Mood States (McNair et al. 1971; 1981) and Withdrawal Symptoms Checklists (Hughes & Hatsukami, 1986).

The impact of tobacco withdrawal on sleep disturbance is potentially crucial to understanding the effects of nicotine deprivation on mood, arousal and daytime drowsiness. Although no clear differences were found between the addicted and non-

addicted smoker groups in terms of changes in mood or arousal following withdrawal, levels of nicotine dependence were correlated with magnitude of increases in "sleep disturbance" and "restlessness" (Chapter 6). These findings are interpreted as suggesting that when dependent smokers abstain from tobacco they have difficulty relaxing or "switching off". Although sleep latency is acutely reduced following smoking cessation (Soldatos et al. 1980; Prosise et al. 1994), withdrawal has been found to increase the number of arousals, awakenings and sleep stage changes (Prosise et al. 1994; Wetter et al. 1995). As suggested, this withdrawal-induced sleep fragmentation could contribute to other withdrawal symptoms, particularly those pertaining to mood and arousal.

In Chapter 7, addicted smokers were shown to rate their alertness and hedonic tone (visual analogue scales) and 'Vigour' (POMS factor) lower when tobacco withdrawn than when non-deprived. Increased ratings of 'impatience', 'excessive yawning' and 'fitful sleep' were also observed following withdrawal. These can readily be presented as evidence of withdrawal-induced sleep disturbance. Ideally, studies should be carried out in order to examine how much impact sleep disturbance has on the other symptoms of the tobacco withdrawal syndrome. If sleep were improved during smoking cessation, residual effects of poor sleep on alertness and mood might be reduced and the probability of continued smoking cessation increased.

The precise mechanism by which nicotine withdrawal disrupts sleep is unknown, although fluctuations of neurotransmitter (particularly noradrenaline and dopamine) levels may be responsible. NRT has been shown to help with withdrawal-induced sleep disturbance (Wetter et al. 1995), but also to cause or exacerbate sleep problems

(Fagerström et al, 1990; Glover, 1993). As discussed in section 8.6, it might be pertinent to examine the benefits of chronic α2-adrenoceptor agonist (e.g. lofexidine) administration. If the sedative side-effects of these drugs can be used with clinical effect and the damping down of excess frontal noradrenaline could mitigate the sleep fragmentation, α2-adrenoceptor agonists could be useful in ameliorating the tobacco withdrawal syndrome in a variety of ways.

Although sleep disturbance may have an important role in many of the mood and arousal effects of nicotine withdrawal, the alerting effect of nicotine when administered via inhalator (Chapter 7) suggests that fragmented sleep resulting from abstinence does not explain the entire relationship. The relevance of this finding is undermined by the concomitant presence of a placebo effect, suggesting that oral stimulation or "sham smoking" may be alerting in itself, regardless of the presence of nicotine.

Many of the negative affect and reduced hedonic tone symptoms associated with abstinence are likely to be direct effects of withdrawal. NRT is still probably the most effective way of treating mood problems caused by withdrawal. Addicted smokers in the current research did not rate hedonic tone significantly greater following the administration of a nicotine inhalator, but these findings were explained in terms of a dosage possibly insufficient to create that effect.

8.6 The role of anxiety and stress in tobacco dependence

The relationship between anxiety and smoking is perhaps one of the most interesting relationships to be addressed by this research. Although anxiety is included as an

established symptom of the tobacco withdrawal syndrome (Hughes & Hatsukami, 1986), more recent formulations of nicotine withdrawal argue that anxiety is ultimately reduced by smoking cessation (West & Hajek, 1997).

Addicted smokers Anxiety factor scores on the Middlesex Health Questionnaire were higher than those of non-addicted smokers and non-smokers, suggesting that tobacco dependent subjects have greater trait anxiety than those who are not tobacco dependent (see Chapter 5). Examining how addicted smokers' anxiety levels change during periods of abstinence could elucidate whether this chronic anxiety may be a result of persistent smoking. It is possible that the observed higher "baseline" levels of anxiety are a result of repeated episodes of nicotine withdrawal and reinstatement throughout each day.

Anxiety ratings measured by factorised visual analogue scales were higher in addicted smokers and lower in non-addicted smokers following twenty-four hour withdrawal (see Chapter 3). When anxiety was measured as an individual checklist item, addicted and non-addicted smokers responses to withdrawal did not differ. The visual analogue scales were completed contingently with cognitive performance tasks. This may suggest that addicted smokers are more neurotic than non-addicted smokers or non-smokers, and were therefore primarily anxious about their task performance in particular, rather than experiencing increased generalised anxiety as a result of their tobacco withdrawal.

However, the addicted smokers examined in Chapter 7 rated their anxiety higher following withdrawal both as an individual checklist item and on the visual analogue

scales (the latter as a non-significant trend). Furthermore, the POMS 'Tension' factor was rated higher by these subjects following the 24-hour abstinence period. The findings from Chapter 7 suggest that addicted smokers' general anxiety levels increase in tobacco withdrawal.

It is still unclear whether increases in anxiety observed in addicted smokers during a period of abstinence is definitively a symptom of tobacco withdrawal, or in fact a return to baseline (pre-smoking) high levels of anxiety which these individuals attempt to self-medicate using nicotine. Although nicotine has not been formally demonstrated to have genuine anxiolytic effects, smokers' reports of their subjective experience often include the calming or anxiety-reducing abilities of cigarettes. Previous research has also shown an association between tobacco dependence and anxiety (Covey et al. 1998). Prospective studies are necessary to investigate whether anxious individuals are prone to developing tobacco dependence, or whether becoming a dependent smoker leads to increased levels of anxiety.

Regardless of the aetiology, increased anxiety following smoking cessation is clearly a problem since it could lead to relapse. Even if, as West & Hajek (1997) suggest, anxiety eventually drops lower than "pre-quit" levels, there is still a 'danger period' where temporary increases in anxiety could affect smoking behaviour. Managing the anxiety component of withdrawal could be one potential explanation for the efficacy of bupropion as a smoking cessation aid. Other drugs with anxiolytic effects such as α2-adrenoceptor agonists could also have positive effects on tobacco withdrawal, and should be investigated.

On a related point, addicted and non-addicted smokers were shown not to differ in terms of levels of perceived stress. This is notable, particularly in light of the divergence between the groups in terms of both baseline and withdrawal levels of anxiety. When combined, the smoker groups had significantly higher levels of perceived stress than non-smokers. If Parrott's (2000) theory that smoking causes stress via the persistent cycle of withdrawal and reinstatement is correct, results presented in Chapter 5 would suggest that non-addicted as well as addicted smokers should experience increased anxiety and tension during tobacco withdrawal. As discussed earlier, results in Chapter 3 show that non-addicted smokers actually rate anxiety lower following withdrawal. Although unlikely, this could be explained by a foreshortened withdrawal syndrome in non-addicted smokers whereby several symptoms, including anxiety, have possibly been and gone before the 24-hour withdrawal period measures were taken.

The relationship between stress or anxiety and tobacco dependence is clearly extremely important in understanding the tobacco withdrawal syndrome, and the addiction to smoking per se. Prospective studies are urgently required in order to fully elucidate the nature of this relationship. Future research of this kind could have important clinical relevance, since reducing smoking prevalence could reduce stress, or identifying groups at risk and reducing their stress or anxiety levels could reduce smoking prevalence.

8.7 Noradrenergic involvement in nicotine addiction

Recent research has shown that noradrenergic structures in dependent smokers are different to those of non-smokers (Klimek et al. 2001). The locus coeruleus' of long-

term smokers were shown to have significantly lower radioligand binding to α2-adrenoceptors than locus coeruleus' (LC) of non-smokers, suggesting lower receptor density in smokers.

It is currently unclear whether these findings demonstrate that individuals with fewer α2-adrenoceptors are more prone to developing tobacco dependence and therefore become smokers, or whether long-term smoking somehow reduces the density of α2-adrenoceptors in the LC, possibly by receptor down-regulation. If the findings reflect long-term effects of smoking on noradrenergic biochemistry, smoking-induced changes in LC activity may strengthen the smoking habit, particularly in people with anxiety or depressive disorders (Klimek et al. 2001).

If smokers are self-medicating with nicotine principally in order to manage negative affect, the modulation of noradrenergic function could be one method by which this is achieved. If chronic smoking down-regulates α2-adrenoceptors in the LC, it is most likely that there will be an increase in noradrenergic activity in this brain structure. In terms of direct effects, this could potentially indicate an acute anti-depressant effect of nicotine.

How this theory relates to the cycle of withdrawal and reinstatement associated with habitual smoking is unclear. It is possible that altered noradrenergic biochemistry, particularly in the LC, is a long-term result of repeated episodes of withdrawal. Opiate withdrawal, for example, is associated with hyperactivity of noradrenergic cells (Brunning et al. 1986) and is successfully managed using α2-adrenoceptor agonists such as clonidine and lofexidine (Gerra et al. 2001). These drugs reduce noradrenergic

activity, particularly in the LC, and this in turn inhibits sympathetic outflow. Excessive sympathetic activity gives rise to many of the observed symptoms of opiate withdrawal.

When abstinent (withdrawn) addicted smokers were administered lofexidine (see Chapter 7), withdrawal symptoms including anxiety and impatience were attenuated, and POMS 'Tension' factor items were rated lower. Furthermore, there was a trend for tobacco cravings to also be reduced following lofexidine. These findings suggest a potential role for lofexidine in managing some aspects of the tobacco withdrawal syndrome.

There are obvious theoretical difficulties when comparing the findings of Klimek et al. (2001) and those of the current studies. If smokers are managing negative affect by using nicotine to increase noradrenergic activity in the LC, administering a drug such as lofexidine, which decreases noradrenergic activity in the LC, could in some instances intensify mood-based withdrawal symptoms. Resolution of this problem may lie in a putative selective action of lofexidine on some subtypes of a2-adrenoceptors (Aoki et al. 1994). This may mean that lofexidine can reduce the subjective perception of withdrawal symptoms and improve the affective reaction during drug withdrawal without the involvement of monoaminergic functions underlying arousal, mood and cardiovascular responses (Gerra et al. 2001).

More research is needed to understand how noradrenergic function relates to both the direct mood and arousal effects of smoking and the tobacco withdrawal syndrome. Crucial to this advancement will be identifying whether the observed reduced α2-

adrenoceptor density in smokers' LC is (a) a result of chronic smoking, or (b) a genetically determined risk factor for tobacco dependence. For example, it could be investigated as to whether chippers, or non-addicted smokers, are protected from tobacco dependence by having relatively higher densities of α2-adrenoceptors prior to the initiation of smoking behaviour.

8.8 Dopaminergic involvement in nicotine addiction

As with the majority of addictive or compulsive behaviours, dopamine has been afforded a central role in the development and maintenance of tobacco smoking behaviour. Specifically, the positive reinforcement aspects of nicotine dependence are ascribed to stimulation of the mesolimbic dopamine system. Although nicotine does not act directly on dopamine receptors, nAChRs found on dopaminergic neurons have been shown to enhance the release of dopamine when stimulated (Reavill, 1990).

Shiffman (1991) proposed that individuals who were more sensitive to the effects of nicotine were more likely to go on to become dependent smokers. It is possible that those who are most sensitive to nicotine initially derive the greatest dopaminergic activity from smoking tobacco. Individual differences in neurobiology of dopaminergic systems could represent one mechanism for variations in responses to nicotine.

Genetic profiles of receptor subtypes provide one means of examining individual differences in human neurotransmitter function *in vivo*. The findings presented in Chapter 4 only support a moderate role for genetically mediated dopaminergic neurobiology in predisposing individuals to nicotine addiction. Dopamine receptor

subtypes D2, D3 and D4 were profiled in non-smokers, addicted smokers and non-addicted smokers. In absolute terms, none of the receptor genotype polymorphisms differed significantly between the three groups of subjects.

The absence of an association between DRD2 polymorphism and smoking behaviour was not consistent with some previous research (Noble et al. 1994), although an observable trend was emerging for addicted smokers to be more likely to possess the A2/A2 genotype. This association has only been previously demonstrated in a Japanese population, which is notable since genetic profiling studies are known to be highly sensitive to ethnic sampling. The fact that no Caucasian sample prior to this study has displayed an association between homozygous DRD2*A2 genotype and tobacco dependence suggests these findings may be a statistical artefact.

However, possession of the DRD4 L-allele was associated with higher Novelty Seeking trait scores on Cloninger's (1993) Temperament and Character Inventory, consistent with much previous research (Ebstein et al.1996). Novelty Seeking scores, and particularly the Impulsivity subscale thereof, were significantly higher in the addicted smokers group, again consistent with previous research (Mitchell, 1999).

These results suggest that dopaminergic neurobiology may have a predisposing effect on smoking behaviour, but it is subtle and the effect is expressed primarily through heritable biologically mediated personality characteristics. When examining the findings of the thesis as a whole, this is theoretically sound. Major differences in dopamine receptor morphology might explain differences in positive reinforcement,

perhaps mediated by relative differences in activity on the nucleus accumbens or another structure in the mesolimbic dopamine pathway.

However, as demonstrated in Chapter 6, non-addicted and addicted smokers differ more significantly in their negative reinforcement responses to tobacco withdrawal and reinstatement. Levels of positive reinforcement, possibly affected by dopamine receptor polymorphisms, are more likely to impact on initial sensitivity to nicotine and therefore be much more important to smoking initiation rather than smoking persistence (Shiffman, 1991). Although neurobiological parameters are important, personality characteristics such as novelty seeking or impulsive tendencies are less likely to be simplistically governed by variations in dopaminergic function. Likewise, the mechanisms of negative reinforcement, i.e. withdrawal psychopharmacology, are more likely to be mediated by other neurotransmitters such as noradrenaline or 5-HT.

In terms of differentiating who is likely to become tobacco dependent, heritable differences in dopaminergic neurobiology may only have a limited role. Although dopamine may be important in the initiation of smoking, differences in heritable personality characteristics may be the only tangible way that dopamine impacts on smoking persistence, hence tobacco dependence.

8.9 Methodological issues

Several methodological limitations have been raised during the discussion sections of each individual chapter. Perhaps the most self-evident and ubiquitous of these issues has been the sample sizes used. Despite the large number of participants who

completed the initial questionnaire study used to develop the Addiction Index score, less than half these subjects went on to perform the experimental studies.

Furthermore, the way that initial sample was split into addicted smokers and non-addicted smokers created unequal group sizes. Although this was a true reflection of the sample, it meant that the addicted smokers group was relatively small. This may have adversely affected statistical procedures by obscuring more subtle differences between the two groups of smokers.

Recruiting addicted smokers for use in the study presented in Chapter 7 was also difficult. A larger number of subjects would have again been preferable for this study, although the within subjects design meant this was less of an issue than with between subjects comparisons featured in earlier chapters.

Although the grouping strategy utilised in Chapters 2 to 6 may be valid for use with this sample, the cut-point of Addiction Index scores of 8 or higher indicating "addicted smoker" status might not be generalisable to other populations, in particular non-student populations. Further work is necessary to examine how robust this cut-point is, or indeed whether the emerging bi-modal distribution discussed in Chapter 2 features in frequency profiles of Addiction Index scores in other samples.

The expectation of smoking following experimental sessions may have affected subjects' performance on cognitive tasks and mood ratings in Chapters 3, 6 and 7. In order to establish the impact of this expectation, further studies should be performed. These would have similar designs and aims, but with a further condition applied

whereby subjects are either informed or uninformed as to whether they will be allowed to smoke following each test session.

A final consideration is the use of the CO breathalyser to ascertain abstinence from smoking. Although readings of less than 10 parts per million breath CO was accepted as indicating compliance with the 24-hour abstinence protocol, these levels could easily be reached through overnight abstinence (approximately 8 hours) in lighter smokers. If subjects had only abstained overnight, withdrawal-induced cognitive performance deficits would not have peaked (Snyder, Davis & Henningfield, 1989), diminishing performance differences between sessions. The CO breathalyser method was chosen because of its convenience and simplicity, but future research should perhaps use plasma nicotine or salivary cotinine levels with appropriate baseline measures to determine abstinence.

8.10 Conclusions

Using a multi-disciplinary approach to studying addiction to smoking it has been possible to ascertain several crucial elements helping to understand the phenomenon. Tobacco dependence appears to be driven by negative rather than positive reinforcement, with the tobacco withdrawal syndrome central to motivating the persistence of the habit. Smokers who are not tobacco dependent show a variety of personality and behavioural differences to their addicted counterparts. These differences may protect them from becoming dependent, or may diminish or disappear if and when tobacco dependence develops.

Anxiety, both trait in terms of personality and state in terms of response to tobacco withdrawal is a crucial component of nicotine addiction. By extraction, addicted smokers appear to be using nicotine to manage anxious symptoms arising through periods of tobacco withdrawal, and possibly self-medicating anxious tendencies inherent in their personalities. The anxiety component of the tobacco withdrawal syndrome may be mediated by relative increases in frontal noradrenaline, particularly in the locus coeruleus, a brain structure implicated in fear and anxiety responses. Lofexidine, an α2-adrenoceptor agonist which reduces noradrenergic activity in this region can be used to mitigate symptoms associated with tobacco withdrawal. This drug could potentially be used as an adjunct or alternative to nicotine replacement therapy in managing the tobacco withdrawal syndrome and improving the chances of successful smoking cessation.

REFERENCES

Abbot, N. C., Stead, L. F., White, A. R., Barnes, J., & Ernst, E. (1999). Hypnotherapy for smoking cessation (Cochrane Review). In *The Cochrane Library, Issue 2.* Update Software: Oxford.

Abrams, D. B., Monti, P. M., Pinto, R. P., Elder, J. P., Brown, R. A., & Jacobus, S. I. (1987). Psychosocial stress and coping in smokers who relapse or quit. *Health Psychol, 6*(4), 289-303.

Acquas, E., Carboni, E., Leone, P., & Di Chiara, G. (1989). SCH 23390 blocks drug-conditioned place-preference and place-aversion: anhedonia (lack of reward) or apathy (lack of motivation) after dopamine-receptor blockade? *Psychopharmacology, 99*(2), 151-5.

Adem, A., Synnergren, B., Botros, M., Ohman, B., Winblad, B., & Nordberg, A. (1987). [3H]acetylcholine nicotinic recognition sites in human brain: characterization of agonist binding. *Neurosci Lett, 83*(3), 298-302.

Aghajanian, G. K. (1978). Tolerance of locus coeruleus neurones to morphine and suppression of withdrawal response by clonidine. *Nature, 276*(5684), 186-8.

Akhurst, J. S. (1999). The use of lofexidine by drug dependency units in the United Kingdom. *Eur Addict Res, 5*(1), 43-9.

Alexander, B. K., & Hadaway, P. F. (1982). Opiate addiction: the case for an adaptive orientation. *Psychol Bull, 92*(2), 367-81.

Allen, S. S., Hatsukami, D., Christianson, D., & Brown, S. (2000). Effects of transdermal nicotine on craving, withdrawal and premenstrual symptomatology in short-term smoking abstinence during different phases of the menstrual cycle. *Nicotine Tob Res, 2*(3), 231-41.

Alpern, H. P., & Jackson, S. J. (1978). Short-term memory: a neuropharmacologically distinct process. *Behav Biol, 22*(2), 133-46.

American Psychiatric Association (1995). *Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition. APA: Washington.

Anda, R. F., Williamson, D. F., Escobedo, L. G., Mast, E. E., Giovino, G. A., & Remington, P. L. (1990). Depression and the dynamics of smoking. A national perspective. *JAMA, 264*(12), 1541-5.

Andersson, K. (1975). Effects of cigarette smoking on learning and retention. *Psychopharmacologia, 41,* 1-5.

Andersson, K. & Hockey, G. (1977). Effects of cigarette smoking on incidental memory. *Reports from the Dept. of Psychology no. 455*, University of Stockholm: Stockholm.

Andrews, N., Hogg, S., Gonzalez, L. E., & File, S. E. (1994). 5-HT1A receptors in the median raphe nucleus and dorsal hippocampus may mediate anxiolytic and anxiogenic behaviours respectively. *Eur J Pharmacol, 264*(3), 259-64.

Arinami, T., Ishiguro, H., & Onaivi, E. S. (2000). Polymorphisms in genes involved in neurotransmission in relation to smoking. *Eur J Pharmacol, 410*(2-3), 215-226.

Armitage, A. K., & Hall, G. H. (1969). Mode of action of intravenous nicotine in causing a fall of blood pressure in the cat. *Eur J Pharmacol, 7*(1), 23-30.

Armitage, A. K., Hall, G. H., & Morrison, C. F. (1968). Pharmacological basis for the tobacco smoking habit. *Nature, 217*(126), 331-4.

Armitage, A. K., Hall, G. H., & Sellers, C. M. (1969). Effects of nicotine on electrocortical activity and acetylcholine release from the cat cerebral cortex. *Br J Pharmacol, 35*(1), 152-60.

Arnsten, A. F., & Goldman-Rakic, P. S. (1985). Alpha 2-adrenergic mechanisms in prefrontal cortex associated with cognitive decline in aged nonhuman primates. *Science, 230*(4731), 1273-6.

Arnsten, A. F., & Cai, J. X. (1993). Postsynaptic alpha-2 receptor stimulation improves memory in aged monkeys: indirect effects of yohimbine versus direct effects of clonidine. *Neurobiol Aging, 14*(6), 597-603.

Ascher, J. A., Cole, J. O., Colin, J. N., Feighner, J. P., Ferris, R. M., Fibiger, H. C., Golden, R. N., Martin, P., Potter, W. Z., Richelson, E., & et al. (1995). Bupropion: a review of its mechanism of antidepressant activity. *J Clin Psychiatry, 56*(9), 395-401.

Asghari, V., Schoots, O., van Kats, S., Ohara, K., Jovanovic, V., Guan, H. C., Bunzow, J. R., Petronis, A., & Van Tol, H. H. (1994). Dopamine D4 receptor repeat: analysis of different native and mutant forms of the human and rat genes. *Mol Pharmacol, 46*(2), 364-73.

Ashton, H., & Golding, J. F. (1989). Smoking: motivation and models. In *Smoking and human behaviour (eds. T. Ney & A. Gale)*, 21-56. John Wiley: Chichester.

Ashton, H., Marsh, V. R., Millman, J. E., Rawlins, M. D., Telford, R., & Thompson, J. W. (1980). Biphasic dose-related responses of the CNV (contingent negative variation) to I.V. nicotine in man. *Br J Clin Pharmacol, 10*(6), 579-89.

Ashton, H., Millman, J. E., Telford, R., & Thompson, J. W. (1974). The effect of caffeine, nitrazepam and cigarette smoking on the contingent negative variation in man. *Electroenceph Clin Neur, 37*(1), 59-71.

Ashton, H., & Stepney, R. (1982). *Smoking: psychology and pharmacology.* Tavistock Publications: London.

Ashton, H., & Watson, D. W. (1970). Puffing frequency and nicotine intake in cigarette smokers. *Br Med J, 3*(724), 679-81.

Bailey, S. L., Ennett, S. T., & Ringwalt, C. L. (1993). Potential mediators, moderators, or independent effects in the relationship between parents' former and current cigarette use and their children's cigarette use. *Addict Behav, 18*(6), 601-21.

Baldinger, B., Hasenfratz, M., & Battig, K. (1995). Comparison of the effects of nicotine on a fixed rate and a subject- paced version of the rapid information processing task. *Psychopharmacology (Berl), 121*(3), 396-400.

Balfour, D. J. (1984). The effects of nicotine on brain neurotransmitter systems. In *Nicotine and the tobacco smoking habit* (ed. D. Balfour). The International Encyclopaedia of Pharmacology and Therapeutics, Section 114. Pergamon Press: Oxford, 61-74.

Balfour, D. J., Benwell, M. E., Birrell, C. E., Kelly, R. J., & Al-Aloul, M. (1998). Sensitization of the mesoaccumbens dopamine response to nicotine. *Pharmacol Biochem Behav, 59*(4), 1021-30.

Balfour, D. J., Birrell, C. E., Moran, R. J., & Benwell, M. E. (1996). Effects of acute D-CPPene on mesoaccumbens dopamine responses to nicotine in the rat. *Eur J Pharmacol, 316*(2-3), 153-6.

Balfour, D. J., & Fagerstrom, K. O. (1996). Pharmacology of nicotine and its therapeutic use in smoking cessation and neurodegenerative disorders. *Pharmacol Ther, 72*(1), 51-81.

Balfour, D. J., Graham, C. A., & Vale, A. L. (1986). Studies on the possible role of brain 5-HT systems and adrenocortical activity in behavioural responses to nicotine and diazepam in an elevated X-maze. *Psychopharmacology, 90*(4), 528-32.

Bates, T., Mangan, G., Stough, C., & Corballis, P. (1995). Smoking, processing speed and attention in a choice reaction time task. *Psychopharmacology (Berl), 120*(2), 209-12.

Bau, C. H., Roman, T., Almeida, S., & Hutz, M. H. (1999). Dopamine D4 receptor gene and personality dimensions in Brazilian male alcoholics. *Psychiatr Genet, 9*(3), 139-43.

Bausell, R. B. (1986). Health-seeking behaviors: public versus public health perspectives. *Psychol Rep, 58*(1), 187-90.

Benjamin, J., Li, L., Patterson, C., Greenberg, B. D., Murphy, D. L., & Hamer, D. H. (1996). Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nat Genet, 12*(1), 81-4.

Benowitz, N. L. (1988). Drug therapy. Pharmacologic aspects of cigarette smoking and nicotine addition. *N Engl J Med, 319*(20), 1318-30.

Benowitz, N. L., Dempsey, D. A., Goldenberg, R. L., Hughes, J. R., Dolan-Mullen, P., Ogburn, P. L., Oncken, C., Orleans, C. T., Slotkin, T. A., Whiteside, H. P., Jr., & Yaffe, S. (2000). The use of pharmacotherapies for smoking cessation during pregnancy. *Tob Control, 9*(Suppl 3), III91-4.

Benowitz, N. L., Jacob, P., 3rd. & Savanapridi, C. (1987). Determinants of nicotine intake while chewing nicotine procrilax gum. *Clin Pharmacol Ther, 41*(5), 467-73.

Benowitz, N. L., & Jacob, P., 3rd. (1994). Metabolism of nicotine to cotinine studied by a dual stable isotope method. *Clin Pharmacol Ther, 56*(5), 483-93.

Benowitz, N. L., & Wilson Peng, W. (2000). Non-nicotine pharmacotherapy for smoking cessation: mechanisms and prospects. *CNS Drugs, 13*(4), 265-85.

Benwell, M. E., & Balfour, D. J. (1979). Effects of nicotine administration and its withdrawal on plasma corticosterone and brain 5-hydroxyindoles. *Psychopharmacology (Berl), 63*(1), 7-11.

Benwell, M. E., & Balfour, D. J. (1982). The effects of nicotine administration on 5-HT uptake and biosynthesis in rat brain. *Eur J Pharmacol, 84*(1-2), 71-7.

Benwell, M. E., & Balfour, D. J. (1997). Regional variation in the effects of nicotine on catecholamine overflow in the rat brain. *Eur J Pharmacol, 325*(1), 13-20.

Benwell, M. E., Balfour, D. J., & Anderson, J. M. (1988). Evidence that tobacco smoking increases the density of (-)-[3H]nicotine binding sites in human brain. *J Neurochem, 50*(4), 1243-7.

Benwell, M. E., Balfour, D. J., & Anderson, J. M. (1990). Smoking-associated changes in the serotonergic systems of discrete regions of human brain. *Psychopharmacology, 102*(1), 68-72.

Benwell, M. E., Balfour, D. J., & Birrell, C. E. (1995). Desensitization of the nicotine-induced mesolimbic dopamine responses during constant infusion with nicotine. *Br J Pharmacol, 114*(2), 454-60.

Benwell, M. E., Balfour, D. J., & Lucchi, H. M. (1993). Influence of tetrodotoxin and calcium on changes in extracellular dopamine levels evoked by systemic nicotine. *Psychopharmacology, 112*(4), 467-74.

Benwell, M. E., & Balfour, J. K. (1985). Nicotine binding to brain tissue from drug-naive and nicotine-treated rats. *J Pharm Pharmacol, 37*(6), 405-9.

Bergen, A. W., & Caporaso, N. (1999). Cigarette smoking. *J Natl Cancer Inst, 91*(16), 1365-75.

Bergen, A. W., Korczak, J. F., Weissbecker, K. A., & Goldstein, A. M. (1999). A genome-wide search for loci contributing to smoking and alcoholism. *Genet Epidemiol, 17*(S1), S55-60.

Berntson, G. G., Beattie, M. S., & Walker, J. M. (1976). Effects of nicotinic and muscarinic compounds on biting attack in the cat. *Pharmacol Biochem Behav, 5*(3), 235-9.

Berkman, L. F. (1984). Assessing the physical health effects of social networks and social support. *Ann Rev Pub Health, 5*(2), 413-32.

Bierut, L. J., Rice, J. P., Edenberg, H. J., Goate, A., Foroud, T., Cloninger, C. R., Begleiter, H., Conneally, P. M., Crowe, R. R., Hesselbrock, V., Li, T. K., Nurnberger, J. I., Jr., Porjesz, B., Schuckit, M. A., & Reich, T. (2000). Family-based study of the association of the dopamine D2 receptor gene (DRD2) with habitual smoking. *Am J Med Genet, 90*(4), 299-302.

Blazer, D. G. (1982). Social support and mortality in an elderly community population. *Am J Epidem, 115*(5), 684-94.

Blum, K., Noble, E. P., Sheridan, P. J., Montgomery, A., Ritchie, T., Jagadeeswaran, P., Nogami, H., Briggs, A. H., & Cohn, J. B. (1990). Allelic association of human dopamine D2 receptor gene in alcoholism. *JAMA, 263*(15), 2055-60.

Boomsma, D. I., Koopmans, J. R., Van Doornen, L. J., & Orlebeke, J. F. (1994). Genetic and social influences on starting to smoke: a study of Dutch adolescent twins and their parents. *Addiction, 89*(2), 219-26.

Brauer, L. H., Hatsukami, D., Hanson, K., & Shiffman, S. (1996). Smoking topography in tobacco chippers and dependent smokers. *Addict Behav, 21*(2), 233-8.

Brazell, M. P., Mitchell, S. N., Joseph, M. H., & Gray, J. A. (1990). Acute administration of nicotine increases the in vivo extracellular levels of dopamine, 3,4-dihydroxyphenylacetic acid and ascorbic acid preferentially in the nucleus accumbens of the rat: comparison with caudate-putamen. *Neuropharmacology, 29*(12), 1177-85.

Breese, C. R., Marks, M. J., Logel, J., Adams, C. E., Sullivan, B., Collins, A. C., & Leonard, S. (1997). Effect of smoking history on [3H]nicotine binding in human postmortem brain. *J Pharmacol Exp Ther, 282*(1), 7-13.

Brioni, J. D., O'Neil, A. B., Kim, D. J., Buckley, M. J., et al. (1994). Anxiolytic-like effects of the novel cholinergic channel activator, ABT-418. *J Pharmacol Exp Therap 271*(2), 352-61.

Broadbent, D. E. (1984). Performance and its measurement. *Br J Clin Pharmacol, 18*(Suppl 1), 5S-11S.

Broadbent, D. E., Broadbent, M. H., Phillpotts, R. J., & Wallace, J. (1984). Some further studies on the prediction of experimental colds in volunteers by psychological factors. *J Psychosom Res, 28*(6), 511-23.

Broadbent, D. E., Cooper, P. F., FitzGerald, P., & Parkes, K. R. (1982). The Cognitive Failures Questionnaire (CFQ) and its correlates. *Br J Clin Psychol, 21*(Pt 1), 1-16.

Brockwell, N. T., & Beninger, R. J. (1996). The differential role of A1 and A2 adenosine receptor subtypes in locomotor activity and place conditioning in rats. *Behav Pharmacol, 7*(4), 373-383.

Brown, R. A., Lewinsohn, P. M., Seeley, J. R. & Wagner, E. F. (1996). Cigarette smoking, major depression, and other psychiatric disorders among adolescents. *J Am Acad Child Adol Psychiatr, 35*(12), 1602-10.

Brunning, J., Mumford, J. P., & Keaney, F. P. (1986). Lofexidine in alcohol withdrawal states. *Alcohol Alcohol, 21*(2), 167-70.

Budney, A. J., Higgins, S. T., Hughes, J. R., & Bickel, W. K. (1993). Nicotine and caffeine use in cocaine-dependent individuals. *J Subst Abuse, 5*(2), 117-30.

Budowle, B., Chakraborty, R., Giusti, A. M., Eisenberg, A. J., & Allen, R. C. (1991). Analysis of the VNTR locus D1S80 by the PCR followed by high-resolution PAGE. *Am J Hum Genet, 48*(1), 137-44.

Burns, B. H. (1969). Chronic chest disease, personality, and success in stopping cigarette smoking. *Br J Prey Soc Med 23,* 23.

Cadoret, R. J., Troughton, E., O'Gorman, T. W., & Heywood, E. (1986). An adoption study of genetic and environmental factors in drug abuse. *Arch Gen Psychiatry, 43*(12), 1131-6.

Carlson, L. E., Goodey, E., Bennett, M. H., Taenzer, P., & Koopmans, J. (2002). The addition of social support to a community-based large-group behavioral smoking cessation intervention: improved cessation rates and gender differences. *Addict Behav, 27*(4), 547-59.

Carmelli, D., Swan, G. E., Robinette, D., & Fabsitz, R. (1992). Genetic influence on smoking--a study of male twins. *N Engl J Med, 327*(12), 829-33.

Carton, S., Jouvent, R., & Widlocher, D. (1994). Sensation seeking, nicotine dependence, and smoking motivation in female and male smokers. *Addict Behav, 19*(3), 219-27.

Cattell, R. B. (1947). Confirmation and clarification of the primary personality factors. *Psychometrika, 12,* 197-220.

Chait, L. D., & Griffiths, R. R. (1983). Effects of caffeine on cigarette smoking and subjective response. *Clin Pharmacol Ther, 34*(5), 612-22.

Chamberlain, K. & O'Neill, D. (1998) Understanding social class differences in health: a qualitative analysis of smokers' health beliefs. *Psychol Health, 13*(6), 1105-19.

Chang, F. M., Kidd, J. R., Livak, K. J., Pakstis, A. J., & Kidd, K. K. (1996). The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. *Hum Genet, 98*(1), 91-101.

Church, R. E. (1989). Smoking and the human EEG. In *Smoking and human behaviour (eds. T. Ney & A. Gale)*, 115-40. John Wiley: Chichester.

Clark, C. R., Geffen, G. M., & Geffen, L. B. (1989). Catecholamines and the covert orientation of attention in humans. *Neuropsychologia, 27*(2), 131-9.

Clarke, P. B. (1991). Nicotinic receptor blockade therapy and smoking cessation. *Br J Addict, 86*(4), 501-5.

Clarke, P. B. (1998). Tobacco smoking, genes, and dopamine. *Lancet, 352*(9122), 84-5.

Clarke, P. B., & Kumar, R. (1983). The effects of nicotine on locomotor activity in non- tolerant and tolerant rats. *Br J Pharmacol, 78*(2), 329-37.

Clarke, P. B., & Pert, A. (1985). Autoradiographic evidence for nicotine receptors on nigrostriatal and mesolimbic dopaminergic neurons. *Brain Res, 348*(2), 355-8.

Clarke, P. B., & Reuben, M. (1996). Release of [3H]-noradrenaline from rat hippocampal synaptosomes by nicotine: mediation by different nicotinic receptor subtypes from striatal [3H]-dopamine release. *Br J Pharmacol, 117*(4), 595-606.

Cloninger, C. R. (1987). A systematic method for clinical description and classification of personality variants. A proposal. *Arch Gen Psychiatry, 44*(6), 573-88.

Cloninger, C. R. (1994). Temperament and personality. *Curr Opin Neurobiol, 4*(2), 266-73.

Cloninger, C. R., Svrakic, D. M., & Przybeck, T. R. (1993). A psychobiological model of temperament and character. *Arch Gen Psychiatry, 50*(12), 975-90.

Cohen, S., & Hoberman, H. M. (1983). Positive events and social support as buffers of life change stress. *J Appl Soc Psychol, 13*(2), 99-125.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *J Health Soc Behav, 24*(4), 385-96.

Cohen, S., Mermelstein, R., Kamarck, T., & Hoberman, H. M. (1985). Measuring the functional components of social support. In *Social support: theory, research and applications.* (eds. I. & B. Sarason). Martinus Nijhoff: Dordrecht.

Cohen, S., Schwartz, J. E., Bromet, E. J., & Parkinson, D. K. (1991). Mental health, stress, and poor health behaviours in two community samples. *Prev Med, 20*(2), 306-15.

Cohen, S., Tyrell, D. A. J., & Smith, A. P. (1993) Life events, perceived stress, negative affect and susceptibility to the common cold. *J Pers Soc Psychol, 64,* 131-40.

Cohen, S., & Wills, T. A. (1985). Stress, social support, and the buffering hypothesis. *Psychol Bull, 98*(2), 310-57.

Cohen, S., & Williamson, G. M. (1991). Stress and infectious diseases in humans. *Psychol Bull, 109*(1), 5-24.

Coleman, P. D. & Flood, D. G. (1987). Neuron numbers and dendritic extent in normal aging and Alzheimer's disease. *Neurobiol Aging, 8,* 521-45.

Coleman, T. (2001). Smoking cessation: integrating recent advances into clinical practice. *Thorax, 56*(7), 579-82.

Comings, D. E. (1998). Polygenic inheritance and micro/minisatellites. *Mol Psychiatry, 3*(1), 21-31.

Comings, D. E., Ferry, L., Bradshaw-Robinson, S., Burchette, R., Chiu, C., & Muhleman, D. (1996a). The dopamine D2 receptor (DRD2) gene: a genetic risk factor in smoking. *Pharmacogenetics, 6*(1), 73-9.

Comings, D. E., Gade-Andavolu, R., Gonzalez, N., Wu, S., Muhleman, D., Blake, H., Dietz, G., Saucier, & MacMurray, J. (1998). Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. *Mol Psychiatry, 2*(1), 44-56.

Comings, D. E., Gade, R., Wu, S., Chiu, C., Dietz, G., Muhleman, D., Saucier, G., Ferry, L., Rosenthal, R. J., Lesieur, H. R., Rugle, L. J., & MacMurray, P. (1997). Studies of the potential role of the dopamine D1 receptor gene in addictive behaviors. *Mol Psychiatry, 2*(1), 44-56.

Comings, D. E., Gonzalez, N., Wu, S., Saucier, G., Johnson, P., Verde, R., & MacMurray, J. P. (1999). Homozygosity at the dopamine DRD3 receptor gene in cocaine dependence. *Mol Psychiatry, 4*(5), 484-7.

Comings, D. E., Rosenthal, R. J., Lesieur, H. R., Rugle, L. J., Muhleman, D., Chiu, C., Dietz, G., & Gade, R. (1996b). A study of the dopamine D2 receptor gene in pathological gambling. *Pharmacogenetics, 6*(3), 223-34.

Conrad, K. M., Flay, B. R., & Hill, D. (1992). Why children start smoking cigarettes: predictors of onset. *Br J Addict, 87*(12), 1711-24.

Corrigall, W. A., & Coen, K. M. (1991). Selective dopamine antagonists reduce nicotine self-administration. *Psychopharmacology, 104*(2), 171-6.

Corrigall, W. A., Franklin, K. B., Coen, K. M., & Clarke, P. B. (1992). The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. *Psychopharmacology, 107*(2-3), 285-9.

Costa, P. T., Jr., & McCrae, R. R. (1997). Stability and change in personality assessment: the revised NEO Personality Inventory in the year 2000. *J Pers Assess, 68*(1), 86-94.

Coull, J. T. (1994). Pharmacological manipulations of the alpha 2-noradrenergic system. Effects on cognition. *Drugs Aging, 5*(2), 116-26.

Coull, J. T., Middleton, H. C., Robbins, T. W., & Sahakian, B. J. (1995). Clonidine and diazepam have differential effects on tests of attention and learning. *Psychopharmacology (Berl), 120*(3), 322-32.

Covey, L. S., Glassman, A. H., & Stetner, F. (1990). Depression and depressive symptoms in smoking cessation. *Compr Psychiatry, 31*(4), 350-4.

Covey, L. S., Glassman, A. H., & Stetner, F. (1998). Cigarette smoking and major depression. *J Addict Dis, 17*(1), 35-46.

Covey, L. S., Sullivan, M. A., Johnston, J. A., Glassman, A. H., Robinson, M. D., & Adams, D. P. (2000). Advances in non-nicotine pharmacotherapy for smoking cessation. *Drugs, 59*(1), 17-31.

Cromwell, J., Bartosch, W. J., Fiore, M. C., Hasselblad, V., & Baker, T. (1997). Cost-effectiveness of the clinical practice recommendations in the AHCPR guideline for smoking cessation. Agency for Health Care Policy and Research. *JAMA, 278*(21), 1759-66.

Crow, T. J. (1968). Cortical synapses and reinforcement: a hypothesis. *Nature, 219,* 736-7.

Crown, S. & Crisp, A. H. (1979). *Manual of the Crown-Crisp experiential index.* Hodder & Stoughton: London.

Dallongeville, J., Marecaux, N., Fruchart, J. C., & Amouyel, P. (1998). Cigarette smoking is associated with unhealthy patterns of nutrient intake: a meta-analysis. *J Nutr, 128*(9), 1450-7.

Dani, J. A., & Heinemann, S. (1996). Molecular and cellular aspects of nicotine abuse. *Neuron, 16*(5), 905-8.

Davies, G. M., Willner, P., & Morgan, M. J. (2000). Smoking-related cues elicit craving in tobacco "chippers": a replication and validation of the two-factor structure of the Questionnaire of Smoking Urges. *Psychopharmacology (Berl), 152*(3), 334-42.

Davies, G. M., Willner, P., James, D. L. & Morgan, M. J. (in press). Influence of nicotine gum on acute craving for cigarettes.

Dawe, S., Gerada, C., Russell, M. A., & Gray, J. A. (1995). Nicotine intake in smokers increases following a single dose of haloperidol. *Psychopharmacology (Berl), 117*(1), 110-5.

Degenhardt, L., Hall, W., & Lynskey, M. (2001). Alcohol, cannabis and tobacco use among Australians: a comparison of their associations with other drug use and use disorders, affective and anxiety disorders, and psychosis. *Addiction, 96*(11), 1603-14.

Depue, R. A., & Collins, P. F. (1999). Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. *Behav Brain Sci, 22*(3), 491-517: discussion 518-69.

Di Chiara, G. (1999). Drug addiction as dopamine-dependent associative learning disorder. *Eur J Pharmacol, 375*(1-3), 13-30 Special Issue.

Duaux, E., Gorwood, P., Griffon, N., Bourdel, M. C., Sautel, F., Sokoloff, P., Schwartz, J. C., Ades, J., Loo, H., & Poirier, M. F. (1998). Homozygosity at the dopamine D3 receptor gene is associated with opiate dependence. *Mol Psychiatry, 3*(4), 333-6.

Duggirala, R., Almasy, L., & Blangero, J. (1999). Smoking behavior is under the influence of a major quantitative trait locus on human chromosome 5q. *Genet Epidemiol, 17*(Suppl 1), S139-44.

Dunn, W. L. (1978). Smoking as a possible inhibitor of arousal. In *Behavioural effects of nicotine* (ed. K. Battig). S. Karger: Basel.

Ebstein, R. P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., Bennett, E. R., Nemanov, L., Katz, M., & Belmaker, R. H. (1996). Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nat Genet, 12*(1), 78-80.

Ekelund, J., Lichtermann, D., Jarvelin, M. R., & Peltonen, L. (1999). Association between novelty seeking and the type 4 dopamine receptor gene in a large Finnish cohort sample. *Am J Psychiatry, 156*(9), 1453-5.

Elgerot, A. (1976). Note on selective effects of short-term tobacco-abstinence on complex versus simple mental tasks. *Percept Mot Skills, 42*(2), 413-4.

Elgerot, A. (1978). Psychological and physiological changes during tobacco-abstinence in habitual smokers. *J Clin Psychol, 34*(3), 759-64.

Emurian, H. H., Nellis, M. J., Brady, J. V., & Ray, R. L. (1982). Event time-series relationship between cigarette smoking and coffee drinking. *Addict Behav, 7*(4), 441-4.

Etter, J. F., Duc, T. V., & Perneger, T. V. (1999). Validity of the Fagerstrom test for nicotine dependence and of the Heaviness of Smoking Index among relatively light smokers. *Addiction, 94*(2), 269-81.

Etter, J. F., & Perneger, T. V. (1999). A comparison of two measures of stage of change for smoking cessation. *Addiction, 94*(12), 1881-9.

Eysenck, H. J. (1980). *The causes and effects of smoking*. Maurice Temple Smith: London.

Eysenck, H. J. & Eysenck, S. B. G. (1964). *Manual of the Eysenck Personality Inventory*. University of London Press: London.

Fagerstrom, K. O. (1978). Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addict Behav, 3*(3-4), 235-41.

Fagerstrom, K. O., & Schneider, N. G. (1989). Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. *J Behav Med, 12*(2), 159-82.

Fagerstrom, K. O., Schneider, N. G., & Lunell, E. (1993). Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. *Psychopharmacology, 111*(3), 271-7.

Feldman, S., & Weidenfeld, J. (1996). Involvement of amygdalar alpha adrenoceptors in hypothalamo-pituitary- adrenocortical responses. *Neuroreport, 7*(18), 3055-7.

Ferry, L. H., & Burchette, R. J. (1994). Efficacy of bupropion for smoking cessation in non-depressed smokers. *J Addict Dis 13,* A9.

Fiore, M. C. (2000). US public health service clinical practice guideline: treating tobacco use and dependence. *Respir Care, 45*(10), 1200-62.

Fleming, J. S. & Watts, W. A. (1981). The dimensionality of self-esteem: some results for a college sample. *J Pers Soc Psychol, 39,* 921-929.

Foulds, J., Stapleton, J., Swettenham, J., Bell, N., McSorley, K., & Russell, M. A. (1996). Cognitive performance effects of subcutaneous nicotine in smokers and never-smokers. *Psychopharmacology (Berl), 127*(1), 31-8.

Freeth, S. (1998). Smoking-related behaviour and attitudes, 1997. *A report on research using the Omnibus Survey produced on behalf of the Department of Health.* Office for National Statistics: London.

Frith, C. D. (1971). Smoking behaviour and its relation to the smoker's immediate experience. *Br J Soc Clin Psychol, 10*(1), 73-8.

Frith, C. D., Dowdy, J., Ferrier, I. N., & Crow, T. J. (1985). Selective impairment of paired associate learning after administration of a centrally-acting adrenergic agonist (clonidine). *Psychopharmacology, 87*(4), 490-3.

Fu, Y., Matta, S. G., James, T. J., & Sharp, B. M. (1998). Nicotine-induced norepinephrine release in the rat amygdala and hippocampus is mediated through brainstem nicotinic cholinergic receptors. *J Pharmacol Exp Ther, 284*(3), 1188-96.

Fu, Y., Matta, S. G., Valentine, J. D., & Sharp, B. M. (1997). Adrenocorticotropin response and nicotine-induced norepinephrine secretion in the rat paraventricular nucleus are mediated through brainstem receptors. *Endocrinology, 138*(5), 1935-43.

Gelernter, J., Kranzler, H., Coccaro, E., Siever, L., New, A., & Mulgrew, C. L. (1997). D4 dopamine-receptor (DRD4) alleles and novelty seeking in substance- dependent, personality-disorder, and control subjects. *Am J Hum Genet, 61*(5), 1144-52.

Gerra, G., Zaimovic, A., Giusti, F., Di Gennaro, C., Zambelli, U., Gardini, S., & Delsignore, R. (2001). Lofexidine versus clonidine in rapid opiate detoxification. *J Subst Abuse Treat, 21*(1), 11-7.

Gilbert, D. G. & Welser, R. (1989). Emotion, anxiety and smoking. In *Smoking and human behaviour (eds. T. Ney & A. Gale)*, 171-96. John Wiley: Chichester.

Gilbert, D. G., Estes, S. L., & Welser, R. (1997). Does noise stress modulate effects of smoking/nicotine? Mood, vigilance, and EEG responses. *Psychopharmacology (Berl), 129*(4), 382-9.

Gilbert, D. G., Robinson, J. H., Chamberlain, C. L., & Spielberger, C. D. (1989). Effects of smoking nicotine on anxiety, heart-rate, and lateralization of EEG during a stressful movie. *Psychophysiology, 26*(3), 311-20.

Glassman, A. H., Jackson, W. K., Walsh, B. T., Roose, S. P., & Rosenfeld, B. (1984). Cigarette craving, smoking withdrawal, and clonidine. *Science, 226*(4676), 864-6.

Gold, M. S., Redmond, D. E., & Kleber, H. D. (1978). Clonidine blocks acute opiate withdrawal symptoms. *Lancet, 2*, 599-602.

Golding, J. F., Harper, T. & Brent-Smith, H. (1983). Personality, drinking and drug-taking correlates of cigarette smoking. *Pers Indiv Diff, 4*(4), 703-6.

Golding, J. F., & Mangan, G. L. (1982). Effects of cigarette smoking on measures of arousal, response suppression, and excitation/inhibition balance. *Int J Addict, 17*(5), 793-804.

Goldstein, A. (1987). Criteria of a pharmacologic withdrawal syndrome. *Arch Gen Psychiatry, 44*(4), 392.

Gould, T. J., Collins, A. C., & Wehner, J. M. (2001). Nicotine enhances latent inhibition and ameliorates ethanol-induced deficits in latent inhibition. *Nicotine Tob Res, 3*(1), 17-24.

Gourlay, S. G., & Benowitz, N. L. (1995). Is clonidine an effective smoking cessation therapy? *Drugs, 50*(2), 197-207.

Gowing, L. R., Farrell, M., Ali, R. L., & White, J. M. (2002). Alpha2-adrenergic agonists in opioid withdrawal. *Addiction, 97*(1), 49-58.

Grady, S., Marks, M. J., Wonnacott, S., & Collins, A. C. (1992). Characterization of nicotinic receptor-mediated [3H]dopamine release from synaptosomes prepared from mouse striatum. *J Neurochem, 59*(3), 848-56.

Grady, S. R., Meinerz, N. M., Cao, J., Reynolds, A. M., Picciotto, M. R., Changeux, J. P., McIntosh, J. M., Marks, M. J., & Collins, A. C. (2001). Nicotinic agonists stimulate acetylcholine release from mouse interpeduncular nucleus: a function mediated by a different nAChR than dopamine release from striatum. *J Neurochem, 76*(1), 258-68.

Gray, J. E. (1973). Dimensions of personality and meaning in self-ratings of personality. *Br J Soc Clin Psychol, 12*(3), 319-22.

Gross, J., & Stitzer, M. L. (1989). Nicotine replacement: ten-week effects on tobacco withdrawal symptoms. *Psychopharmacology, 98*(3), 334-41.

Gurling, H. M., Grant, S., & Dangl, J. (1985). The genetic and cultural transmission of alcohol use, alcoholism, cigarette smoking and coffee drinking: a review and an example using a log linear cultural transmission model. *Br J Addict, 80*(3), 269-79.

Haddad, L. G., & Malak, M. Z. (2002). Smoking habits and attitudes towards smoking among university students in Jordan. *Int J Nurs Stud, 39*(8), 793-802.

Hahn, B., Shoaib, M., & Stolerman, I. P. (2002). Nicotine-induced enhancement of attention in the five-choice serial reaction time task: the influence of task demands. *Psychopharmacology (Berl), 162*(2), 129-37.

Hajek, P. (1989). Withdrawal-oriented therapy for smokers. *Br J Addict, 84*(6), 591-8.

Hajek, P., West, R., & Wilson, J. (1995). Regular smokers, lifetime very light smokers, and reduced smokers: comparison of psychosocial and smoking characteristics in women. *Health Psychol, 14*(3), 195-201.

Hall, G. H. (1970). Effects of nicotine and tobacco smoke on the electrical activity of the cerebral cortex and olfactory bulb. *Br J Pharmacol, 38*(2), 271-86.

Hall, G. H., & Turner, D. M. (1972). Effects of nicotine on the release of 3 H-noradrenaline from the hypothalamus. *Biochem Pharmacol, 21*(13), 1829-38.

Hatsukami, D., Hughes, J. R., & Pickens, R. (1985). Characterization of tobacco withdrawal: physiological and subjective effects. *NIDA Res Monogr, 53*, 56-67.

Hatsukami, D. K., Dahlgren, L., Zimmerman, R., & Hughes, J. R. (1988). Symptoms of tobacco withdrawal from total cigarette cessation versus partial cigarette reduction. *Psychopharmacology, 94*(2), 242-7.

Hatsukami, D. K., Hughes, J. R., Pickens, R. W., & Svikis, D. (1984). Tobacco withdrawal symptoms: an experimental analysis. *Psychopharmacology, 84*(2), 231-6.

Heath, A. C. (1990). Persist or quit? Testing for a genetic contribution to smoking persistence. *Acta Genet Med Gemellol, 39*(4), 447-58.

Heath, A. C., Madden, P. A., Slutske, W. S., & Martin, N. G. (1995). Personality and the inheritance of smoking behavior: a genetic perspective. *Behav Genet, 25*(2), 103-17.

Heath, A. C., & Madden, P. A. (1985). Genetic influences on smoking behaviour. In *Genetic Approaches in Behavioral Medicine* (eds. L. Cardon & J. Hewitt). Plenum Press: New York, 45-66.

Heath, A. C., & Martin, N. G. (1993). Genetic models for the natural history of smoking: evidence for a genetic influence on smoking persistence. *Addict Behav, 18*(1), 19-34.

Heimstra, N. W. (1973). The effects of smoking on mood change. In *Smoking behaviour: motives and incentives* (ed. W. L. Dunn), 197-207. Winston: Washington.

Heimstra, N. W., Fallesen, J. J., Kinsley, S. A., & Warner, N. W. (1980). The effects of deprivation of cigarette smoking on psychomotor performance. *Ergonomics, 23*(11), 1047-55.

Heishman, S. J., Taylor, R. C., & Henningfield, J.E. (1994). Nicotine and smoking: a review of effects on human performance. *Exp Clin Psychopharmacol, 2*(3), 345-95.

Heishman, S. J. (1998). What aspects of human performance are truly enhanced by nicotine? *Addiction, 93*(3), 317-20.

Heishman, S. J., & Henningfield, J. E. (2000). Tolerance to repeated nicotine administration on performance, subjective, and physiological responses in nonsmokers. *Psychopharmacology (Berl), 152*(3), 321-33.

Hellstrom-Lindahl, E., Gorbounova, O., Seiger, A., Mousavi, M., & Nordberg, A. (1999). Regional distribution of nicotinic receptors during prenatal development of human brain and spinal cord. *Brain Res Dev Brain Res, 108*(1-2), 147-60.

Hellstrom-Lindahl, E., Mousavi, M., Zhang, X., Ravid, R., & Nordberg, A. (1999). Regional distribution of nicotinic receptor subunit mRNAs in human brain: comparison between Alzheimer and normal brain. *Brain Res Mol Brain Res, 66*(1-2), 94-103.

Henderson, S. (1981). Social relationships, adversity and neurosis: an analysis of prospective observations. *Br J Psychiatry, 138*, 391-8.

Henningfield, J. E., Fant, R. V., Gitchell, J., & Shiffman, S. (2000). Tobacco dependence. Global public health potential for new medications development and indications. *Ann N Y Acad Sci, 909*, 247-56.

Herbst, J. H., Zonderman, A. B., McCrae, R. R., & Costa, P. T., Jr. (2000). Do the dimensions of the temperament and character inventory map a simple genetic architecture? Evidence from molecular genetics and factor analysis. *Am J Psychiatry, 157*(8), 1285-90.

Herxheimer, A. (1967). Circulatory effects of nicotine aerosol inhalations and cigarette smoking in man. *Lancet, 2*(7519), 754-5.

Hill, P., & Wynder, E. L. (1974). Smoking and cardiovascular disease. Effect of nicotine on the serum epinephrine and corticoids. *Am Heart J, 87*(4), 491-6.

Hillefors-Berglund, M., Hedlund, P. B., & von Euler, G. (1995). Effects of CGS 21680 in vivo on dopamine D2 agonist binding in the rat brain. *Brain Res, 690*(1), 34-40.

Hirschman, R. S., Leventhal, H., & Glynn, K. (1984). The development of smoking behaviour - conceptualization and supportive cross-sectional survey data. *J Appl Soc Psychol, 14*(3), 184-206.

Holm, K. J., & Spencer, C. M. (2000). Bupropion: a review of its use in the management of smoking cessation. *Drugs, 59*(4), 1007-24.

Houlihan, M. E., Pritchard, W. S., & Robinson, J. H. (1996). Faster P300 latency after smoking in visual but not auditory oddball tasks. *Psychopharmacology (Berl), 123*(3), 231-8.

Hughes, J. R. (1992). Tobacco withdrawal in self-quitters. *J Consult Clin Psychol, 60*(5), 689-97.

Hughes, J. R., Goldstein, M. G., Hurt, R. D., & Shiffman, S. (1999a). Recent advances in the pharmacotherapy of smoking. *JAMA, 281*(1), 72-6.

Hughes, J. R., Gust, S. W., & Pechacek, T. F. (1987). Prevalence of tobacco dependence and withdrawal. *Am J Psychiatry, 144*(2), 205-8.

Hughes, J. R., & Hatsukami, D. (1985). Short-term effects of nicotine gum. *NIDA Res Monogr, 53*, 68-82.

Hughes, J. R., & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry, 43*(3), 289-94.

Hughes, J. R., Hatsukami, D. K., Mitchell, J. E., & Dahlgren, L. A. (1986). Prevalence of smoking among psychiatric outpatients. *Am J Psychiatry, 143*(8), 993-7.

Hughes, J. R., Hatsukami, D. K., Pickens, R. W., Krahn, D., Malin, S., & Luknic, A. (1984). Effect of nicotine on the tobacco withdrawal syndrome. *Psychopharmacology, 83*(1), 82-7.

Hughes, J. R., Higgins, S. T., & Bickel, W. K. (1994). Nicotine withdrawal versus other drug withdrawal syndromes: similarities and dissimilarities. *Addiction, 89*(11), 1461-70.

Hughes, J. R., Higgins, S. T., & Hatsukami, D. (1990). Effects of abstinence from tobacco: a critical review. In *Recent advances in alcohol and drug problems, Vol.10* (eds. T. Kozlowski & H. Annis). Plenum Press: New York, 317-98.

Hughes, J. R., Lesmes, G. R., Hatsukami, D. K., Richmond, R. L., Lichtenstein, E., Jorenby, D. E., Broughton, J. O., Fortmann, S. P., Leischow, S. J., McKenna, J. P., Rennard, S. I., Wadland, W. C., & Heatley, S. A. (1999b). Are higher doses of nicotine replacement more effective for smoking cessation? *Nicotine Tob Res, 1*(2), 169-74.

Hughes, J. R., Stead, L. F., & Lancaster, T. (2002). Antidepressants for smoking cessation. *Cochrane Database Syst Rev, 1*.

Hurt, R. D., Sachs, D. P., Glover, E. D., Offord, K. P., Johnston, J. A., Dale, L. C., Khayrallah, M. A., Schroeder, D. R., Glover, P. N., Sullivan, C. R., Croghan, I. T., & Sullivan, P. M. (1997). A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med, 337*(17), 1195-202.

Hymowitz, N., Feuerman, M., Hollander, M., & Frances, R. J. (1993). Smoking deterrence using silver acetate. *Hosp Community Psychiatry, 44*(2), 113-4, 118.

Ikard, F. F., Green, D. E., & Horn, D. (1969). A scale to differentiate between types of smoking as related to the management of affect. *Int J Addict 4*(5), 649-59.

Imperato, A., Mulas, A., & Di Chiara, G. (1986). Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats. *Eur J Pharmacol, 132*(2-3), 337-8.

Isbell, H. & White, W. M. (1953). Clinical characteristics of addictions. *JAMA, 14,* 558-65.

Ishiguro, H., Okuyama, Y., Toru, M., & Arinami, T. (2000a). Mutation and association analysis of the 5' region of the dopamine D3 receptor gene in schizophrenia patients: identification of the Ala38Thr polymorphism and suggested association between DRD3 haplotypes and schizophrenia. *Mol Psychiatry, 5*(4), 433-8.

Ishiguro, H., Saito, T., Shibuya, H., & Arinami, T. (2000b). Association study between genetic polymorphisms in the 14-3-3 eta chain and dopamine D4 receptor genes and alcoholism. *Alcohol Clin Exp Res, 24*(3), 343-7.

Istvan, J., & Matarazzo, J. D. (1984). Tobacco, alcohol, and caffeine use: a review of their interrelationships. *Psychol Bull, 95*(2), 301-26.

Iwamoto, E. T. (1990). Nicotine conditions place preferences after intracerebral administration in rats. *Psychopharmacology, 100*(2), 251-7.

Jackson, P. H., Stapleton, J. A., Russell, M. A., & Merriman, R. J. (1986). Predictors of outcome in a general practitioner intervention against smoking. *Prev Med, 15*(3), 244-53.

Jaffe, J. H. (1980). Drug addiction and drug abuse. In *The pharmacological basis of therapeutics* (eds. A. G. Gilman, L. Goodman & A. Gilman). Macmillan: New York, 535-607.

Jarvik, M. E. (1967). Tobacco smoking in monkeys. *Ann NY Acad Sci, 5*, 196-200.

Jarvik, M. E., Caskey, N. H., Wirshing, W. C., Madsen, D. C., Iwamoto-Schaap, P. N., Elins, J. L., Eisenberger, N. I., & Olmstead, R. E. (2000a). Bromocriptine reduces cigarette smoking. *Addiction, 95*(8), 1173-83.

Jarvik, M. E., Madsen, D. C., Olmstead, R. E., Iwamoto-Schaap, P. N., Elins, J. L., & Benowitz, N. L. (2000b). Nicotine blood levels and subjective craving for cigarettes. *Pharmacol Biochem Behav, 66*(3), 553-8.

Jarvis, M. J. (1994). A profile of tobacco smoking. *Addiction, 89*(11), 1371-6.

Jenks, R. J. (1992). Attitudes, perceptions, and risk-taking behaviors of smokers, ex-smokers, and nonsmokers. *J Soc Psychol, 132*(5), 569-75.

Johnson, W. L., Malow, R. M., Corrigan, S. A., & West, J. A. (1993). Impulsive behaviour and substance abuse. In *The impulsive client: theory, research and treatment* (eds. W. McCown, J. Johnson & M. Shure). American Psychological Association: Washington D. C.

Jones, G. M., Sahakian, B. J., Levy, R., Warburton, D. M., & Gray, J. A. (1992). Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. *Psychopharmacology, 108*(4), 485-94.

Jonsson, E. G., Nothen, M. M., Grunhage, F., Farde, L., Nakashima, Y., Propping, P., & Sedvall, G. C. (1999). Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Mol Psychiatry, 4*(3), 290-6.

Jonsson, E. G., Nothen, M. M., Gustavsson, J. P., Neidt, H., Forslund, K., Mattila-Evenden, M., Rylander, G., Propping, P., & Asberg, M. (1998). Lack of association between dopamine D4 receptor gene and personality traits. *Psychol Med, 28*(4), 985-9.

Jorenby, D. E., Leischow, S. J., Nides, M. A., Rennard, S. I., Johnston, J. A., Hughes, A. R., Smith, S. S., Muramoto, M. L., Daughton, D. M., Doan, K., Fiore, M. C., & Baker, T. B. (1999). A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med, 340*(9), 685-91.

Kalant, H., LeBlanc, A. E., & Gibbins, R. J. (1971). Tolerance to, and dependence on, some non-opiate psychotropic drugs. *Pharmacol Rev, 23*(3), 135-91.

Kalivas, P. W., Sorg, B. A., & Hooks, M. S. (1993). The pharmacology and neural circuitry of sensitization to psychostimulants. *Behav Pharmacol, 4*(4), 315-334.

Kandel, D. B., & Davies, M. (1986). Adult sequelae of adolescent depressive symptoms. *Arch Gen Psychiatry, 43*(3), 255-62.

Kaprio, J., Sarna, S., Koskenvuo, M., & Rantasalo, I. (1978). *The Finnish Twin Registry: baseline characteristics, Section II.* University of Helsinki Press: Helsinki.

Karras, A., & Kane, J. M. (1980). Naloxone reduces cigarette smoking. *Life Sci, 27*(17), 1541-5.

Kassel, J. D., & Shiffman, S. (1997). Attentional mediation of cigarette smoking's effect on anxiety. *Health Psychol, 16*(4), 359-68.

Kassel, J. D., Shiffman, S., Gnys, M., Paty, J., & Zettler-Segal, M. (1994). Psychosocial and personality differences in chippers and regular smokers. *Addict Behav, 19*(5), 565-75.

Kazmi, M. A., Snyder, L. A., Cypess, A. M., Graber, S. G., & Sakmar, T. P. (2000). Selective reconstitution of human D4 dopamine receptor variants with Gi alpha subtypes. *Biochemistry, 39*(13), 3734-44.

Kerr, J. S., Sherwood, N., & Hindmarch, I. (1991). Separate and combined effects of the social drugs on psychomotor performance. *Psychopharmacology, 104*(1), 113-9.

Kety, S. S. (1970). The biogenic amines in the central nervous system: their possible roles in arousal, emotion and learning. In *Neurosciences second study program* (ed. F. Schmitt). Rockefeller University Press: New York.

Killen, J. D., & Fortmann, S. P. (1997). Craving is associated with smoking relapse: findings from three prospective studies. *Exp Clin Psychopharmacol, 5*(2), 137-42.

Killen, J. D., Fortmann, S. P., Telch, M. J., & Newman, B. (1988). Are heavy smokers different from light smokers? A comparison after 48 hours without cigarettes. *JAMA, 260*(11), 1581-5.

Klimek, V., Zhu, M-Y., Dilley, G., Konick, L., Overholser, J. C., Meltzer, H. Y., May, W. L., Stockmeier, C. A., & Ordway, G. A. (2001). Effects of long-term cigarette smoking on the human locus coeruleus. *Arch Gen Psych, 58,* 821-827.

Knott, V. J. (1989). Brain electrical imaging the dose-response effects of cigarette smoking. *Neuropsychobiology, 22*(4), 236-42.

Knott, V. J., & Venables, P. H. (1977). EEG alpha correlates of non-smokers, smokers, smoking, and smoking deprivation. *Psychophysiology, 14*(2), 150-6.

Koelega, H. S. (1993). Stimulant drugs and vigilance performance: a review. *Psychopharmacology, 111*(1), 1-16.

Koob, G. F. (1992). Drugs of abuse: anatomy, pharmacology and function of reward pathways. *Trends Pharmacol Sci, 13*(5), 177-84.

Kotler, M., Cohen, H., Segman, R., Gritsenko, I., Nemanov, L., Lerer, B., Kramer, I., Zer-Zion, M., Kletz, I., & Ebstein, R. P. (1997). Excess dopamine D4 receptor (D4DR) exon III seven repeat allele in opioid-dependent subjects. *Mol Psychiatry, 2*(3), 251-4.

Kozlowski, L. T. (1981). Application of some physical indicators of cigarette smoking. *Addict Behav, 6*(3), 213-9.

Kuhn, K. U., Meyer, K., Nothen, M. M., Gansicke, M., Papassotiropoulos, A., & Maier, W. (1999). Allelic variants of dopamine receptor D4 (DRD4) and serotonin receptor 5HT2c (HTR2c) and temperament factors: replication tests. *Am J Med Genet, 88*(2), 168-72.

Lancaster, T., & Stead, L. F. (2000). Self-help interventions for smoking cessation. *Cochrane Database Syst Rev, 2.*

Lannfelt, L., Sokoloff, P., Martres, M. P., Pilon, C., Giros, B., Johnsson, E., et al. (1992). Amino acid substitution in the dopamine D3 receptor as a useful polymorphism for investigating psychiatric disorders. *Psychiatr Gen, 34*(2), 285-91.

Lasagna, L., Mosteller, F. von Felsinger, J. M., & Beecher, H. E. (1954). A study of the placebo response. *Am J Med 16,* 770-9.

Le Houezec, J., Halliday, R., Benowitz, N. L., Callaway, E., Naylor, H., & Herzig, K. (1994). A low dose of subcutaneous nicotine improves information processing in non-smokers. *Psychopharmacology (Berl), 114*(4), 628-34.

Leischow, S. J., Valente, S. N., Hill, A. L., Otte, P. S., Aickin, M., Holden, T., Kligman, E., & Cook, G. (1997). Effects of nicotine dose and administration method on withdrawal symptoms and side effects during short-term smoking abstinence. *Exp Clin Psychopharmacol, 5*(1), 54-64.

Lena, C., de Kerchove D'Exaerde, A., Cordero-Erausquin, M., Le Novere, N., del Mar Arroyo-Jimenez, M., & Changeux, J. P. (1999). Diversity and distribution of nicotinic acetylcholine receptors in the locus ceruleus neurons. *Proc Natl Acad Sci U S A, 96*(21), 12126-31.

Lerman, C., Caporaso, N., Main, D., Audrain, J., Boyd, N. R., Bowman, E. D., & Shields, P. G. (1998). Depression and self-medication with nicotine: the modifying influence of the dopamine D4 receptor gene. *Health Psychol, 17*(1), 56-62.

Levin, E. D., & Simon, B. B. (1998). Nicotinic acetylcholine involvement in cognitive function in animals. *Psychopharmacology (Berl), 138*(3-4), 217-30.

Li, T., Xu, K., Deng, H., Cai, G., Liu, J., Liu, X., Wang, R., Xiang, X., Zhao, J., Murray, R. M., Sham, P. C., & Collier, D. A. (1997). Association analysis of the dopamine D4 gene exon III VNTR and heroin abuse in Chinese subjects. *Mol Psychiatry, 2*(5), 413-6.

Li, T., Zhu, Z. H., Liu, X., Hu, X., Zhao, J., Sham, P. C., & Collier, D. A. (2000). Association analysis of polymorphisms in the DRD4 gene and heroin abuse in Chinese subjects. *Am J Med Genet, 96*(5), 616-21.

Lichter, J. B., Barr, C. L., Kennedy, J. L., Van Tol, H. H., Kidd, K. K., & Livak, K. J. (1993). A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. *Hum Mol Genet, 2*(6), 767-73.

Loehlin, J. C. (1992). Using EQS for a simple analysis of the Colorado Adoption Project data on height and intelligence. *Behav Genet, 22*(2), 239-45.

Logue, A. W. (1995). *Self-control: waiting until tomorrow for what you want today.* Prentice Hall: Englewood Cliffs, N. J.

Lu, Y., Grady, S., Marks, M. J., Picciotto, M., Changeux, J. P., & Collins, A. C. (1998). Pharmacological characterization of nicotinic receptor-stimulated GABA release from mouse brain synaptosomes. *J Pharmacol Exp Ther, 287*(2), 648-57.

Lu, Y., Marks, M. J., & Collins, A. C. (1999). Desensitization of nicotinic agonist-induced [3H]gamma-aminobutyric acid release from mouse brain synaptosomes is produced by subactivating concentrations of agonists. *J Pharmacol Exp Ther, 291*(3), 1127-34.

Mancuso, G., Andres, P., Ansseau, M., & Tirelli, E. (1999). Effects of nicotine administered via a transdermal delivery system on vigilance: a repeated measure study. *Psychopharmacology (Berl), 142*(1), 18-23.

Mangan, G. L., & Golding, J. F. (1978). An 'enhancement' model of smoking maintenance. In *Smoking behaviour: physiological and psychological influences* (ed. R. E. Thornton), 87-114.

Mangan, G. L., & Golding, J. F. (1983). The effects of smoking on memory consolidation. *J Psychol, 115*(1st Half), 65-77.

Markou, A., Weiss, F., Gold, L. H., Caine, S. B., Schulteis, G., & Koob, G. F. (1993). Animal models of drug craving. *Psychopharmacology, 112*(2-3), 163-82.

Marks, M. J., Campbell, S. M., Romm, E., & Collins, A. C. (1991). Genotype influences the development of tolerance to nicotine in the mouse. *J Pharmacol Exp Ther, 259*(1), 392-402.

Marks, M. J., Pauly, J. R., Gross, S. D., Deneris, E. S., Hermans-Borgmeyer, I., Heinemann, S. F., & Collins, A. C. (1992). Nicotine binding and nicotinic receptor subunit RNA after chronic nicotine treatment. *J Neurosci, 12*(7), 2765-84.

Marlatt, G. A. & Gordon, J. R. (eds.) (1985). *Relapse prevention - maintenance strategies in the treatment of addictive behaviours.* The Guildford Press: New York.

Marshall, D. L., Redfern, P. H., & Wonnacott, S. (1997). Presynaptic nicotinic modulation of dopamine release in the three ascending pathways studied by in vivo microdialysis: comparison of naive and chronic nicotine-treated rats. *J Neurochem, 68*(4), 1511-9.

Mason, S. T., & Iversen, S. D. (1979). Theories of the dorsal bundle extinction effect. *Brain Res, 180*(1), 107-37.

Mathews, A. (1990). Why worry? The cognitive function of anxiety. *Behav Res Ther, 28*(6), 455-68.

McCown, W. G., Johnson, J. L., & Shure, M. B. (eds.) (1993). *The impulsive client: theory, research and treatment.* American Psychological Association: Washington D. C.

McCrae, R. R., & Costa, P. T., Jr. (1997). Personality trait structure as a human universal. *Am Psychol, 52*(5), 509-16.

McGee, K. H. & Murray, K. M. (1989). Clonidine in nicotine withdrawal. *Dicp Ann Pharmacother, 23*(6), 473-4.

McGehee, D. S., Heath, M. J., Gelber, S., Devay, P., & Role, L. W. (1995). Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. *Science, 269*(5231), 1692-6.

McGehee, D. S., & Role, L. W. (1995). Physiological diversity of nicotinic acetylcholine receptors expressed by vertebrate neurons. *Annu Rev Physiol, 57*, 521-46.

McKennell, A. C. (1970). Smoking motivation factos. *Br J Soc Clin Psychol, 9*(1), 8-22.

McNair, D. M., Lorr, M., & Droppelman, L. F. (1971). *Profile of Mood States Manual.* Educational and Industrial Testing Service: San Diego.

McNair, D. M., Lorr, M., & Droppelman, L. F. (1981). *Profile of Mood States Manual.* Educational and Industrial Testing Service: San Diego.

Medlund, P., Cederlog, R., Floderus-Myrhed, B., Friberg, L. & Sorensen, S. (1977). A new Swedish twin registry. *Acta Med Scand Supp, 600,* 1-11.

Meliska, C. J., & Gilbert, D. G. (1991). Hormonal and subjective effects of smoking the first five cigarettes of the day: a comparison in males and females. *Pharmacol Biochem Behav, 40*(2), 229-35.

Mifsud, J. C., Hernandez, L., & Hoebel, B. G. (1989). Nicotine infused into the nucleus accumbens increases synaptic dopamine as measured by in vivo microdialysis. *Brain Res, 478*(2), 365-7.

Mirza, N. R., & Stolerman, I. P. (1998). Nicotine enhances sustained attention in the rat under specific task conditions. *Psychopharmacology (Berl), 138*(3-4), 266-74.

Miller, W. R., & Gold, M. S. (1998). Comorbid cigarette and alcohol addiction: epidemiology and treatment. *J Addict Dis, 17*(1), 55-66.

Mitchell, S. H. (1999). Measures of impulsivity in cigarette smokers and non-smokers. *Psychopharmacology (Berl), 146*(4), 455-64.

Morgan, M. J., Davies, G. M., & Willner, P. (1999). The Questionnaire of Smoking Urges is sensitive to abstinence and exposure to smoking-related cues. *Behav Pharmacol, 10*(6-7), 619-26.

Mumenthaler, M. S., Taylor, J. L., O'Hara, R., & Yesavage, J. A. (1998). Influence of nicotine on simulator flight performance in non-smokers. *Psychopharmacology (Berl), 140*(1), 38-41.

Myrsten, A. L., Elgerot, A., & Edgren, B. (1977). Effects of abstinence from tobacco smoking on physiological and psychological arousal levels in habitual smokers. *Psychosom Med, 39*(1), 25-38.

Nelsen, J. M. (1978). Psychological consequences of chronic nicotinisation: a focus on arousal. In *Behavioural effects of nicotine* (ed. K. Battig), 1-17. S. Karger: Basel.

Ney, T., & Gale, A. (1989). *Smoking and human behaviour.* John Wiley: Chichester.

Niaura, R., Abrams, D. B., Pedraza, M., Monti, P. M., & Rohsenow, D. J. (1992). Smokers' reactions to interpersonal interaction and presentation of smoking cues. *Addict Behav, 17*(6), 557-66.

Niaura, R., Shadel, W. G., Abrams, D. B., Monti, P. M., Rohsenow, D. J., & Sirota, A. (1998). Individual differences in cue reactivity among smokers trying to quit: effects of gender and cue type. *Addict Behav, 23*(2), 209-24.

Nisell, M., Nomikos, G. G., & Svensson, T. H. (1994a). Infusion of nicotine in the ventral tegmental area or the nucleus accumbens of the rat differentially affects accumbal dopamine release. *Pharmacol Toxicol, 75*(6), 348-52.

Nisell, M., Nomikos, G. G., & Svensson, T. H. (1994b). Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area. *Synapse, 16*(1), 36-44.

Noble, E. P., Blum, K., Khalsa, M. E., Ritchie, T., Montgomery, A., Wood, R. C., Fitch, R. J., Ozkaragoz, T., Sheridan, P. J., Anglin, M. D., & et al. (1993). Allelic association of the D2 dopamine receptor gene with cocaine dependence. *Drug Alcohol Depend, 33*(3), 271-85.

Noble, E. P., St Jeor, S. T., Ritchie, T., Syndulko, K., St Jeor, S. C., Fitch, R. J., Brunner, R. L., & Sparkes, R. S. (1994). D2 dopamine receptor gene and cigarette smoking: a reward gene? *Med Hypotheses, 42*(4), 257-60.

Nordberg, A., Adem, A., Hardy, J., & Winblad, B. (1988). Change in nicotinic receptor subtypes in temporal cortex of Alzheimer brains. *Neurosci Lett, 86*(3), 317-21.

Okuyama, Y., Ishiguro, H., Nankai, M., Shibuya, H., Watanabe, A., & Arinami, T. (2000). Identification of a polymorphism in the promoter region of DRD4 associated with the human novelty seeking personality trait. *Mol Psychiatry, 5*(1), 64-9.

O'Neill, S. T., & Parrott, A. C. (1992). Stress and arousal in sedative and stimulant cigarette smokers. *Psychopharmacology, 107*(2-3), 442-6.

Ong, M. L., Ball, S. G., & Vaughan, P. F. (1991). Regulation of noradrenaline release from rat occipital cortex tissue chops by alpha 2-adrenergic agonists. *J Neurochem, 56*(4), 1387-93.

Ono, Y., Manki, H., Yoshimura, K., Muramatsu, T., Mizushima, H., Higuchi, S., Yagi, G., Kanba, S., & Asai, M. (1997). Association between dopamine D4 receptor (D4DR) exon III polymorphism and novelty seeking in Japanese subjects. *Am J Med Genet, 74*(5), 501-3.

Ornish, S. A., Zisook, S., & McAdams, L. A. (1988). Effects of transdermal clonidine treatment on withdrawal symptoms associated with smoking cessation. A randomized, controlled trial. *Arch Intern Med, 148*(9), 2027-31.

Ornish, S. A., Zisook, S., & McAdams, L. A. (2001). Effects of transdermal clonidine treatment on withdrawal symptoms associated with smoking cessation. A randomized, controlled trial. *Cochrane Database Syst Rev, 1*(9), 2027-31.

Overton, P. G., & Clark, D. (1997). Burst firing in midbrain dopaminergic neurons. *Brain Res Brain Res Rev, 25*(3), 312-34.

Owen, N., Kent, P., Wakefield, M., & Roberts, L. (1995). Low-rate smokers. *Prev Med, 24*(1), 80-4.

Panter, A. T., & Reeve, B. B. (2002). Assessing tobacco beliefs among youth using item response theory models. *Drug Alcohol Depend, 68 Suppl 1*, S21-39.

Parrott, A. C. (1995a). Smoking cessation leads to reduced stress, but why? *Int J Addict, 30*(11), 1509-16.

Parrott, A. C. (1995b). Stress modulation over the day in cigarette smokers. *Addiction, 90*(2), 233-44.

Parrott, A. C. (1998). Nesbitt's Paradox resolved? Stress and arousal modulation during cigarette smoking. *Addiction, 93*(1), 27-39.

Parrott, A. C. (2000). Cigarette smoking does cause stress. *Am Psychol, 55*(10), 1159-60.

Parrott, A. C., & Kaye, F. J. (1999). Daily uplifts, hassles, stresses and cognitive failures: in cigarette smokers, abstaining smokers, and non-smokers. *Behav Pharmacol, 10*(6-7), 639-46.

Parrott, A. C., & Winder, G. (1989). Nicotine chewing gum (2 mg, 4 mg) and cigarette smoking: comparative effects upon vigilance and heart rate. *Psychopharmacology, 97*(2), 257-61.

Paulhus, D. (1983). Sphere-specific measures of perceived control. *J Pers Soc Psychol, 44*(6), 1253-1265.

Payne, T. J., Smith, P. O., Sturges, L. V., & Holleran, S. A. (1996). Reactivity to smoking cues: mediating roles of nicotine dependence and duration of deprivation. *Addict Behav, 21*(2), 139-54.

Peng, X., Gerzanich, V., Anand, R., Whiting, P. J., & Lindstrom, J. (1994). Nicotine-induced increase in neuronal nicotinic receptors results from a decrease in the rate of receptor turnover. *Mol Pharmacol, 46*(3), 523-30.

Perkins, K. A., Epstein, L. H., Stiller, R. L., Sexton, J. E., Debski, T. D., & Jacob, R. G. (1990). Behavioral performance effects of nicotine in smokers and nonsmokers. *Pharmacol Biochem Behav, 37*(1), 11-5.

Perkins, K. A., Grobe, J. E., Fonte, C., Goettler, J., Caggiula, A. R., Reynolds, W. A., Stiller, R. L., Scierka, A., & Jacob, R. G. (1994). Chronic and acute tolerance to subjective, behavioral and cardiovascular effects of nicotine in humans. *J Pharmacol Exp Ther, 270*(2), 628-38.

Perkins, K. A., Grobe, J. E., Weiss, D., Fonte, C., & Caggiula, A. (1996). Nicotine preference in smokers as a function of smoking abstinence. *Pharmacol Biochem Behav, 55*(2), 257-63.

Perkins, K. A., Sexton, J. E., DiMarco, A., Grobe, J. E., Scierka, A., & Stiller, R. L. (1995). Subjective and cardiovascular responses to nicotine combined with alcohol in male and female smokers. *Psychopharmacology (Berl), 119*(2), 205-12.

Perry, E. K., Court, J. A., Johnson, M., Piggott, M. A., & Perry, R. H. (1992). Autoradiographic distribution of [3H]nicotine binding in human cortex: relative abundance in subicular complex. *J Chem Neuroanat, 5*(5), 399-405.

Pianezza, M. L., Sellers, E. M., & Tyndale, R. F. (1998). Nicotine metabolism defect reduces smoking. *Nature, 393*(6687), 750.

Piasecki, T. M., Niaura, R., Shadel, W. G., Abrams, D., Goldstein, M., Fiore, M. C., & Baker, T. B. (2000). Smoking withdrawal dynamics in unaided quitters. *J Abnorm Psychol, 109*(1), 74-86.

Picciotto, M. R., Brunzell, D. H., & Caldarone, B. J. (2002). Effect of nicotine and nicotinic receptors on anxiety and depression. *Neuroreport, 13*(9), 1097-106.

Picciotto, M. R., Caldarone, B. J., King, S. L., & Zachariou, V. (2000). Nicotinic receptors in the brain. Links between molecular biology and behavior. *Neuropsychopharmacology, 22*(5), 451-65.

Pickworth, W. B., Fant, R. V., Butschky, M. F., & Henningfield, J. E. (1996). Effects of transdermal nicotine delivery on measures of acute nicotine withdrawal. *J Pharmacol Exp Ther, 279*(2), 450-6.

Pidoplichko, V. I., De Bias, M., Williams, J. T., & Dani, J. A. (1997). Nicotine activates and desensitises midbrain dopamine neurones. *Nature 390*(3), 401-4.

Pogue-Geile, M., Ferrell, R., Deka, R., Debski, T., & Manuck, S. (1998). Human novelty-seeking personality traits and dopamine D4 receptor polymorphisms: a twin and genetic association study. *Am J Med Genet, 81*(1), 44-8.

Pomerleau, C. S., Pomerleau, O. F., Flessland, K. A., & Basson, S. M. (1992). Relationship of Tridimensional Personality Questionnaire scores and smoking variables in female and male smokers. *J Subst Abuse, 4*(2), 143-54.

Pomerleau, O. F. (1995). Individual differences in sensitivity to nicotine: implications for genetic research on nicotine dependence. *Behav Genet, 25*(2), 161-77.

Pomerleau, O. F., Collins, A. C., Shiffman, S., & Pomerleau, C. S. (1993a). Why some people smoke and others do not: new perspectives. *J Consult Clin Psychol, 61*(5), 723-31.

Pomerleau, O. F., Fertig, J. B., Seyler, L. E., & Jaffe, J. (1983a). Neuroendocrine reactivity to nicotine in smokers. *Psychopharmacology, 81*(1), 61-7.

Pomerleau, O. F., Fertig, J. B., & Shanahan, S. O. (1983b). Nicotine dependence in cigarette smoking: an empirically-based, multivariate model. *Pharmacol Biochem Behav, 19*(2), 291-9.

Pomerleau, O. F., Hariharan, M., Pomerleau, C. S., Cameron, O. G., & Guthrie, S. K. (1993b). Differences between smokers and never-smokers in sensitivity to nicotine: a preliminary report. *Addiction, 88*(1), 113-8.

Pomerleau, O. F., & Pomerleau, C. S. (1988). Nicotine replacement: an overview. *Prog Clin Biol Res, 261*, 279-95.

Pomerleau, O. F., & Pomerleau, C. S. (1989). Stress, smoking, and the cardiovascular system. *J Subst Abuse, 1*(3), 331-43.

Pomerleau, O. F., & Pomerleau, C. S. (1990). Behavioural studies in humans: anxiety, stress and smoking. *Ciba Found Symp, 152*, 225-35.

Pomerleau, O. F., Pomerleau, C. S., & Namenek, R. J. (1998). Early experiences with tobacco among women smokers, ex-smokers, and never-smokers. *Addiction, 93*(4), 595-9.

Pomerleau, O. F., Turk, D. C., & Fertig, J. B. (1984). The effects of cigarette smoking on pain and anxiety. *Addict Behav, 9*(3), 265-71.

Pontieri, F. E., Passarelli, F., Calo, L., & Caronti, B. (1998). Functional correlates of nicotine administration: similarity with drugs of abuse. *J Mol Med, 76*(3-4), 193-201.

Pontieri, F. E., Tanda, G., Orzi, F., & Di Chiara, G. (1996). Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature, 382*(6588), 255-7.

Posner, M. I. (1980). Orienting of attention. *Q J Exp Psychol, 32*(1), 3-25.

Poulos, C. X., & Cappell, H. (1991). Homeostatic theory of drug tolerance: a general model of physiological adaptation. *Psychol Rev, 98*(3), 390-408.

Powell, D. H. (1973). A pilot study of occasional heroin users. *Arch Gen Psychiatry, 28*(4), 586-94.

Presson, C. C., Chassin, L., & Sherman, S. J. (2002). Psychosocial antecedents of tobacco chipping. *Health Psychol, 21*(4), 384-92.

Presti, D. E., Ary, D. V., & Lichtenstein, E. (1992). The context of smoking initiation and maintenance: findings from interviews with youths. *J Subst Abuse, 4*(1), 35-45.

Prochazka, A. V. (2000). New developments in smoking cessation. *Chest, 117*(4 Suppl 1), 169S-175S.

Prochazka, A. V., Petty, T. L., Nett, L., Silvers, G. W., Sachs, D. P., Rennard, S. I., Daughton, D. M., Grimm, R. H., Jr., & Heim, C. (1992). Transdermal clonidine reduced some withdrawal symptoms but did not increase smoking cessation. *Arch Intern Med, 152*(10), 2065-9.

Prosise, G. L., Bonnet, M. H., Berry, R. B., & Dickel, M. J. (1994). Effects of abstinence from smoking on sleep and daytime sleepiness. *Chest, 105*(4), 1136-41.

Reavill, C. (1990). Actions of nicotine on dopaminergic pathways and implications for Parkinson's disease. In *Nicotine pharmacology: molecular, cellular and behavioural aspects* (eds. S. Wonnacott, M. Russell, I. Stolerman), 307-340. Oxford University Press: Oxford.

Reavill, C., & Stolerman, I. P. (1990). Locomotor activity in rats after administration of nicotinic agonists intracerebrally. *Br J Pharmacol, 99*(2), 273-8.

Redmond, D. E., Hwang, Y. H., & Gold, M. S. (1977). "Anxiety: the locus coeruleus connection". *Neurosci Abstr, 3,* 258.

Rehm, J., Fichter, M. M., & Elton, M. (1993). Effects on mortality of alcohol consumption, smoking, physical activity, and close personal relationships. *Addiction, 88*(1), 101-12.

Reitstetter, R., Lukas, R.J., & Gruener, R. (1999). Dependence of nicotinic acetylcholine receptor recovery from desensitization on the duration of agonist exposure. *J Pharmacol Exp Ther, 289*(3), 656-60.

Rennard, S. I., & Daughton, D. M. (2000). Smoking cessation. *Chest, 117*(5 Suppl 2), 360S-4S.

Richter, J., Brandstrom, S., & Przybeck, T. (1999). Assessing personality: the Temperament and Character Inventory in a cross-cultural comparison between Germany, Sweden and the USA. *Psychol Rep, 84*(3), 1315-1330 Part 2.

Rezvani, A. H., & Levin, E. D. (2001). Cognitive effects of nicotine. *Biol Psychiatry, 49*(3), 258-67.

Ridley, D. L., & Balfour, D. J. (1997). The influence of nicotine on 5-HT overflow in the dorsal hippocampus of the rat. *Br J Pharmacol 122*(2), 301.

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev, 18*(3), 247-91.

Rowe, D. C., Chassin, L., Presson, C. C., Edwards, D., & Sherman, S. J. (1992). An epidemic model of adolescent cigarette smoking. *J Appl Soc Psych, 22*(4), 261-85.

Rowell, P. P., Carr, L. A., & Garner, A. C. (1987). Stimulation of [3H]dopamine release by nicotine in rat nucleus accumbens. *J Neurochem, 49*(5), 1449-54.

Rowell, P. P., & Duggan, D. S. (1998). Long-lasting inactivation of nicotinic receptor function in vitro by treatment with high concentrations of nicotine. *Neuropharmacology, 37*(1), 103-11.

Royal College of Physicians, Tobacco Advisory Group (2000). Nicotine Addiction in Britain. Royal College of Physicians: Lavenham Press Ltd.: Sudbury.

Russell, D., Peplau, L. A., & Ferguson, M. L. (1978). Developing a measure of loneliness. *J Pers Assess, 42*(3), 290-4.

Russell, M. A. (1990). The nicotine addiction trap: a 40-year sentence for four cigarettes. *Br J Addict, 85*(2), 293-300.

Russell, M. A., & Feyerabend, C. (1978). Cigarette smoking: a dependence on high-nicotine boli. *Drug Metab Rev, 8*(1), 29-57.

Russell, M. A., Peto, J., & Patel, U. A. (1974). The classification of smoking by factorial structure of motives. *J R Stat Soc A, 137*(3), 313-33.

Russell, M. A., Raw, M., & Jarvis, M. J. (1980). Clinical use of nicotine chewing-gum. *Br Med J, 280*(6231), 1599-602.

Russell, M. A., Stapleton, J. A., Feyerabend, C., Wiseman, S. M., Gustavsson, G., Sawe, U., & Connor, P. (1993). Targeting heavy smokers in general practice: randomised controlled trial of transdermal nicotine patches. *Bmj, 306*(6888), 1308-12.

Rusted, J. M., Graupner, L., & Warburton, D. M. (1995). Effects of post-trial administration of nicotine on human memory: evaluating the conditions for improving memory. *Psychopharmacology (Berl), 119*(4), 405-13.

Rusted, J. M., Graupner, L., Tennant, A., & Warburton, D. M. (1998). Effortful processing is a requirement for nicotine-induced improvements in memory. *Psychopharmacology (Berl), 138*(3-4), 362-8.

Sahakian, B. J., Coull, J. J., & Hodges, J. R. (1994). Selective enhancement of executive function by idazoxan in a patient with dementia of the frontal lobe type. *J Neurol Neurosurg Psychiatry, 57*(1), 120-1.

Sander, T., Harms, H., Dufeu, P., Kuhn, S., Rommelspacher, H., & Schmidt, L. G. (1997). Dopamine D4 receptor exon III alleles and variation of novelty seeking in alcoholics. *Am J Med Genet, 74*(5), 483-7.

Schachter, S., Silverstein, B., Kozlowski, L. T., Perlick, D., Herman, C. P., & Liebling, B. (1977). Studies of the interaction of psychological and pharmacological determinants of smoking. *J Exp Psychol Gen, 106*(1), 3-12.

Schilstrom, B., Svensson, H. M., Svensson, T. H., & Nomikos, G. G. (1998). Nicotine and food induced dopamine release in the nucleus accumbens of the rat: putative role of alpha7 nicotinic receptors in the ventral tegmental area. *Neuroscience, 85*(4), 1005-9.

Schneider, N. G., Olmstead, R., Nilsson, F., Mody, F. V., Franzon, M., & Doan, K. (1996). Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial. *Addiction, 91*(9), 1293-306.

Schultz, W. (1997). Dopamine neurons and their role in reward mechanisms. *Curr Opin Neurobiol, 7*(2), 191-7.

Schultz, W. (2001). Reward signaling by dopamine neurons. *Neuroscientist, 7*(4), 293-302.

Schumann, A., Hapke, U., Rumpf, H. J., Meyer, C., & John, U. (2001). The association between degree of nicotine dependence and other health behaviours. Findings from a German general population study. *Eur J Public Health, 11*(4), 450-2.

Schwartz, R. D., & Kellar, K. J. (1985). In vivo regulation of [3H]acetylcholine recognition sites in brain by nicotinic cholinergic drugs. *J Neurochem, 45*(2), 427-33.

Seckl, J. R., & Fink, G. (1991). Use of in situ hybridization to investigate the regulation of hippocampal corticosteroid receptors by monoamines. *J Steroid Biochem Mol Biol, 40*(4-6), 685-8.

Seevers, M. H. (1962). Medical perspectives on habituation and addiction. *JAMA, 181*, 92-8.

Seltzer, C. C., & Oechsli, F. W. (1985). Psychosocial characteristics of adolescent smokers before they started smoking: evidence of self-selection. A prospective study. *J Chronic Dis, 38*(1), 17-26.

Sharp, B. M., & Matta, S. G. (1993). Detection by in vivo microdialysis of nicotine-induced norepinephrine secretion from the hypothalamic paraventricular nucleus of freely moving rats: dose-dependency and desensitization. *Endocrinology, 133*(1), 11-9.

Shields, P. G., Lerman, C., Audrain, J., Bowman, E. D., Main, D., Boyd, N. R., & Caporaso, N. E. (1998). Dopamine D4 receptors and the risk of cigarette smoking in African- Americans and Caucasians. *Cancer Epidemiol Biomarkers Prev, 7*(6), 453-8.

Shiffman, S. (1989). Tobacco "chippers"--individual differences in tobacco dependence. *Psychopharmacology, 97*(4), 539-47.

Shiffman, S. (1991). Refining models of dependence: variations across persons and situations. *Br J Addict, 86*(5), 611-5.

Shiffman, S. (2000). Comments on craving. *Addiction, 95 Suppl 2*, S171-5.

Shiffman, S. & Balabanis, M. (1996). Do drinking and smoking go together? *Alc Health Res World, 20*(2), 107-10.

Shiffman, S., Engberg, J. B., Paty, J. A., Perz, W. G., Gnys, M., Kassel, J. D., & Hickcox, M. (1997). A day at a time: predicting smoking lapse from daily urge. *J Abnorm Psychol, 106*(1), 104-16.

Shiffman, S., Fischer, L. B., Zettler-Segal, M., & Benowitz, N. L. (1990). Nicotine exposure among nondependent smokers. *Arch Gen Psychiatry, 47*(4), 333-6.

Shiffman, S., Gnys, M., Richards, T. J., Paty, J. A., Hickcox, M., & Kassel, J. D. (1996). Temptations to smoke after quitting: a comparison of lapsers and maintainers. *Health Psychol, 15*(6), 455-61.

Shiffman, S., Gwaltney, C. J., Balabanis, M. H., Liu, K. S., Paty, J. A., Kassel, J. D., Hickcox, M., & Gnys, M. (2002). Immediate antecedents of cigarette smoking: an analysis from ecological momentary assessment. *J Abnorm Psychol, 111*(4), 531-45.

Shiffman, S., Johnston, J. A., Khayrallah, M., Elash, C. A., Gwaltney, C. J., Paty, J. A., Gnys, M., Evoniuk, G., & DeVeaugh-Geiss, J. (2000). The effect of bupropion on nicotine craving and withdrawal. *Psychopharmacology (Berl), 148*(1), 33-40.

Shiffman, S., Kassel, J. D., Paty, J., Gnys, M., & Zettler-Segal, M. (1994). Smoking typology profiles of chippers and regular smokers. *J Subst Abuse, 6*(1), 21-35.

Shiffman, S., Paty, J. A., Gnys, M., Kassel, J. D., & Elash, C. (1995). Nicotine withdrawal in chippers and regular smokers: subjective and cognitive effects. *Health Psychol, 14*(4), 301-9.

Shiffman, S., Shumaker, S. A., Abrams, D. B., Cohen, S., Garvey, A., Grunberg, N. E., & Swan, G. E. (1986). Models of smoking relapse. *Health Psychol, 5*(Suppl), 13-27.

Shiffman, S., Zettler-Segal, M., Kassel, J., Paty, J., Benowitz, N. L., & O'Brien, G. (1992). Nicotine elimination and tolerance in non-dependent cigarette smokers. *Psychopharmacology, 109*(4), 449-56.

Shiffman, S. M. (1979). The tobacco withdrawal syndrome. *NIDA Res Monogr*(23), 158-84.

Shiffman, S. M., & Jarvik, M. E. (1976). Smoking withdrawal symptoms in two weeks of abstinence. *Psychopharmacology (Berl), 50*(1), 35-9.

Shoaib, M., Benwell, M. E., Akbar, M. T., Stolerman, I. P., & Balfour, D. J. (1994). Behavioural and neurochemical adaptations to nicotine in rats: influence of NMDA antagonists. *Br J Pharmacol, 111*(4), 1073-80.

Shoaib, M., Swanner, L. S., Yasar, S., & Goldberg, S. R. (1999). Chronic caffeine exposure potentiates nicotine self-administration in rats. *Psychopharmacology (Berl), 142*(4), 327-33.

Silagy, C., Mant, D., Fowler, G., & Lancaster, T. (2000). Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev, 2*.

Silverstein, B., Kelly, E., Swan, J., & Kozlowski, L. T. (1982). Physiological predisposition toward becoming a cigarette smoker: experimental evidence for a sex difference. *Addict Behav, 7*(1), 83-6.

Singleton, A. B., Thomson, J. H., Morris, C. M., Court, J. A., Lloyd, S., & Cholerton, S. (1998). Lack of association between the dopamine D2 receptor gene allele DRD2*A1 and cigarette smoking in a United Kingdom population. *Pharmacogenetics, 8*(2), 125-8.

Smith, A. P., & Nutt, D. J. (1996). Noradrenaline and attention lapses. *Nature, 380*(6572), 291.

Smith, A. P., Wilson, S. J., Glue, P. & Nutt, D. J. (1992a). The effects and after-effects of the alpha-2-adrenoceptor agonist idazoxan on mood, memory and attention in normal volunteers. *J Psychopharmacol, 6,* 376-81.

Smith, S. S., O'Hara, B. F., Persico, A. M., Gorelick, D. A., Newlin, D. B., Vlahov, D., Solomon, L., Pickens, R., & Uhl, G. R. (1992b). Genetic vulnerability to drug abuse. The D2 dopamine receptor Taq I B1 restriction fragment length polymorphism appears more frequently in polysubstance abusers. *Arch Gen Psychiatry, 49*(9), 723-7.

Snell, W. E., Johnson, G., Lloyd, P. J., & Hoover, M. W. (1991). The health orientation scale - a measure of psychological tendencies associated with health. *Eur J Pers, 5*(2), 169-83.

Snyder, F. R., Davis, F. C., & Henningfield, J. E. (1989). The tobacco withdrawal syndrome: performance decrements assessed on a computerized test battery. *Drug Alcohol Depend, 23*(3), 259-66.

Snyder, F. R., & Henningfield, J. E. (1989). Effects of nicotine administration following 12 h of tobacco deprivation: assessment on computerized performance tasks. *Psychopharmacology, 97*(1), 17-22.

Sommese, T., & Patterson, J. C. (1995). Acute effects of cigarette smoking withdrawal: a review of the literature. *Aviat Space Environ Med, 66*(2), 164-7.

Spitz, M. R., Shi, H., Yang, F., Hudmon, K. S., Jiang, H., Chamberlain, R. M., Amos, C. I., Wan, Y., Cinciripini, P., Hong, W. K., & Wu, X. (1998). Case-control study of the D2 dopamine receptor gene and smoking status in lung cancer patients. *J Natl Cancer Inst, 90*(5), 358-63.

Stapleton, J. A., Russell, M. A., Feyerabend, C., Wiseman, S. M., Gustavsson, G., Sawe, U., & Wiseman, D. (1995). Dose effects and predictors of outcome in a randomized trial of transdermal nicotine patches in general practice. *Addiction, 90*(1), 31-42.

Stewart, S. H., & Kushner, M. G. (2001). Introduction to the Special Issue on "Anxiety Sensitivity and Addictive Behaviors". *Addict Behav, 26*(6), 775-85.

Stolerman, I. P. (1990). Behavioural pharmacology of nicotine: implications for multiple brain nicotinic receptors. *Ciba Found Symp, 152*, 3-16.

Stolerman, I. P., Goldfarb, T., Fink, R., & Jarvik, M. E. (1973). Influencing cigarette smoking with nicotine antagonists. *Psychopharmacologia, 28*(3), 247-59.

Stollery, B. T., Banks, H. A., Broadbent, D. E., & Lee, W. R. (1989). Cognitive functioning in lead workers. *Br J Ind Med, 46*(10), 698-707.

Strang, J., Bearn, J., & Gossop, M. (1999). Lofexidine for opiate detoxification: review of recent randomised and open controlled trials. *Am J Addict, 8*(4), 337-48.

Strobel, A., Wehr, A., Michel, A., & Brocke, B. (1999). Association between the dopamine D4 receptor (DRD4) exon III polymorphism and measures of Novelty Seeking in a German population. *Mol Psychiatry, 4*(4), 378-84.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *J Exp Psych, 18*(3), 643-62.

Sullivan, P. F., Fifield, W. J., Kennedy, M. A., Mulder, R. T., Sellman, J. D., & Joyce, P. R. (1998). No association between novelty seeking and the type 4 dopamine receptor gene (DRD4) in two New Zealand samples. *Am J Psychiatry, 155*(1), 98-101.

Suraway, C. J. & Cox, T. (1987). Smoking under natural conditions: a diary study. *Pers Individ Diff, 8*(1), 33-41.

Sutherland, G., Stapleton, J. A., Russell, M. A., & Feyerabend, C. (1995). Naltrexone, smoking behaviour and cigarette withdrawal. *Psychopharmacology (Berl), 120*(4), 418-25.

Sutherland, G., Stapleton, J. A., Russell, M. A., Jarvis, M. J., Hajek, P., Belcher, M., & Feyerabend, C. (1992). Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet, 340*(8815), 324-9.

Svensson, T. H., Bunney, B. S., & Aghajanian, G. K. (1975). Inhibition of both noradrenergic and serotonergic neurons in brain by the alpha-adrenergic agonist clonidine. *Brain Res, 92*(2), 291-306.

Svensson, T. H., & Strombom, U. (1977). Discontinuation of chronic clonidine treatment: evidence for facilitated brain noradrenergic neurotransmission. *Naunyn Schmiedebergs Arch Pharmacol, 299*(1), 83-7.

Swan, G. E., Ward, M. M., & Jack, L. M. (1996). Abstinence effects as predictors of 28-day relapse in smokers. *Addict Behav, 21*(4), 481-90.

Tanda, G., & Goldberg, S. R. (2000). Alteration of the behavioral effects of nicotine by chronic caffeine exposure. *Pharmacol Biochem Behav, 66*(1), 47-64.

Thomas, C. B. (1973). The relationship of smoking and habits of nervous tension. In *Smoking behaviour: motives and incentives* (ed. W. L. Dunn), 157-70. Winston: Washington.

Tiffany, S.T. (1999). Cognitive concepts of craving. *Alcohol Res Health, 23*(3), 215-24.

Tiffany, S. T., & Drobes, D. J. (1991). The development and initial validation of a questionnaire on smoking urges. *Br J Addict, 86*(11), 1467-76.

Tizabi, Y., Copeland, R. L., Jr., Louis, V. A., & Taylor, R. E. (2002). Effects of combined systemic alcohol and central nicotine administration into ventral tegmental area on dopamine release in the nucleus accumbens. *Alcohol Clin Exp Res, 26*(3), 394-9.

Tomitaka, M., Tomitaka, S., Otuka, Y., Kim, K., Matuki, H., Sakamoto, K., & Tanaka, A. (1999). Association between novelty seeking and dopamine receptor D4 (DRD4) exon III polymorphism in Japanese subjects. *Am J Med Genet, 88*(5), 469-71.

Tonnesen, P., Paoletti, P., Gustavsson, G., Russell, M., et al. (1999). Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. *Eur Resp J 13*(2), 238-46.

True, W. R., Heath, A. C., Scherrer, J. F., Waterman, B., Goldberg, J., Lin, N., Eisen, S. A., Lyons, M. J., & Tsuang, M. T. (1997). Genetic and environmental contributions to smoking. *Addiction, 92*(10), 1277-87.

Turner, R. J., & Marino, F. (1994). Social support and social structure: a descriptive epidemiology. *J Health Soc Behav, 35*(3), 193-212.

Uhde, T. W., Boulenger, J. P., Post, R. M., Siever, L. J., Vittone, B. J., Jimerson, D. C., & Roy-Byrne, P. P. (1984). Fear and anxiety: relationship to noradrenergic function. *Psychopathology, 17*(Suppl 3), 8-23.

Uhde, T. W., Redmond, D. E., Jr., & Kleber, H. D. (1980). Clonidine suppresses the opioid abstinence syndrome without clonidine- withdrawal symptoms: a blind inpatient study. *Psychiatry Res, 2*(1), 37-47.

Ulbrich, P. M., Warheit, G. J., & Zimmerman, R. S. (1989). Race, socioeconomic status, and psychological distress: an examination of differential vulnerability. *J Health Soc Behav, 30*(1), 131-46.

Waingrow, S., & Horn, D. (1968). Relationship of number of cigarettes smoked to "tar" rating. *Natl Cancer Inst Monogr, 28*, 29-33.

Waingrow, S. M., Horn, D., & Ikard, F. F. (1968). Dosage patterns of cigarette smoking in American adults. *Am J Public Health Nations Health, 58*(1), 54-70.

Wankel, L. M., Mummery, W. K., Stephens, T., & Craig, C. L. (1994). Prediction of physical activity intention from social psychological variables - results from the Campbell survey of well-being. *J Sp Exerc Psych, 16*(1), 56-69.

Warburton, D. M. (1988). The puzzle of nicotine use. In *The psychopharmacology of addiction* (ed. M. Lader) Oxford University Press: Oxford.

Warburton, D. M. (1994). The reality of the beneficial effects of nicotine. *Addiction, 89*(2), 138-9; discussion 144-6.

Warburton, D. M., & Arnall, C. (1994). Improvements in performance without nicotine withdrawal. *Psychopharmacology (Berl), 115*(4), 539-42.

Warburton, D. M., & Mancuso, G. (1998). Evaluation of the information processing and mood effects of a transdermal nicotine patch. *Psychopharmacology (Berl), 135*(3), 305-10.

Warburton, D. M., Revell, A., & Walters, A. C. (1988). Nicotine as a resource. In *The pharmacology of nicotine* (eds. M. Rand & K. Thurau). ICSU Press: London, 359-73.

Waters, A. J. & Sutton, S. R. (2000). Direct and indirect effects of nicotine/smoking on cognition in humans. *Addict Behav 25*(1), 29-43

Weiss, F., Ciccocioppo, R., Parsons, L. H., Katner, S., Liu, X., Zorrilla, E. P., Valdez, G. R., Ben-Shahar, O., Angeletti, S., & Richter, R. R. (2001). Compulsive drug-seeking behavior and relapse. Neuroadaptation, stress, and conditioning factors. *Ann N Y Acad Sci, 937*, 1-26.

Welzl, H., Battig, K., & Berz, S. (1990). Acute effects of nicotine injection into the nucleus accumbens on locomotor activity in nicotine-naive and nicotine-tolerant rats. *Pharmacol Biochem Behav, 37*(4), 743-6.

Wesnes, K., & Warburton, D. M. (1978). The effects of cigarette smoke and nicotine upon human attention. In *Smoking behaviour: physiological and psychological influences* (ed. R. Thornton). Churchill Livingstone: Edinburgh, 131-47.

Wesnes, K., & Warburton, D. M. (1983a). Effects of smoking on rapid information processing performance. *Neuropsychobiology, 9*(4), 223-9.

Wesnes, K., & Warburton, D. M. (1983b). Smoking, nicotine and human performance. *Pharmacol Ther, 21*(2), 189-208.

Wesnes, K., & Warburton, D. M. (1984). The effects of cigarettes of varying yield on rapid information processing performance. *Psychopharmacology, 82*(4), 338-42.

West, R. (1992). The 'nicotine replacement paradox' in smoking cessation: how does nicotine gum really work? *Br J Addict, 87*(2), 165-7.

West, R. (2001). Glucose for smoking cessation: does it have a role? *CNS Drugs, 15*(4), 261-5.

West, R., Edwards, M., & Hajek, P. (1998). A randomized controlled trial of a "buddy" systems to improve success at giving up smoking in general practice. *Addiction, 93*(7), 1007-11.

West, R., & Gossop, M. (1994). Overview: a comparison of withdrawal symptoms from different drug classes. *Addiction, 89*(11), 1483-9.

West, R., & Hajek, P. (1997). What happens to anxiety levels on giving up smoking? *Am J Psychiatry, 154*(11), 1589-92.

West, R., McEwen, A., Bolling, K., & Owen, L. (2001). Smoking cessation and smoking patterns in the general population: a 1- year follow-up. *Addiction, 96*(6), 891-902.

West, R., & Schneider, N. (1987). Craving for cigarettes. *Br J Addict, 82*(4), 407-15.

West, R., & Shiffman, S. (2001). Effect of oral nicotine dosing forms on cigarette withdrawal symptoms and craving: a systematic review. *Psychopharmacology (Berl), 155*(2), 115-22.

West, R. J., Hajek, P., & Belcher, M. (1989). Severity of withdrawal symptoms as a predictor of outcome of an attempt to quit smoking. *Psychol Med, 19*(4), 981-5.

West, R. J., & Jarvis, M. J. (1986). Effects of nicotine on finger tapping rate in non-smokers. *Pharmacol Biochem Behav, 25*(4), 727-31.

West, R. J., & Russell, M. A. (1985). Pre-abstinence smoke intake and smoking motivation as predictors of severity of cigarette withdrawal symptoms. *Psychopharmacology, 87*(3), 334-6.

White, A. R., & Rampes, H. (1999). Acupuncture for smoking cessation (Cochrane Review). In *The Cochrane Library, Issue 2*. Update Software: Oxford.

Wikler, A. (1973). Dynamics of drug dependence. Implications of a conditioning theory for research and treatment. *Arch Gen Psychiatry, 28*(5), 611-6.

Williams, A. F. (1973). Personality and other characteristics associated with cigarette smoking among young teenagers. *J Health Soc Behav, 14*(4), 374-80.

Williams, D. G. (1980). Effects of cigarette smoking on immediate memory and performance in different kinds of smoker. *Br J Psychol, 71*(1), 83-90.

Willner, P., Hardman, S., & Eaton, G. (1995). Subjective and behavioural evaluation of cigarette cravings. *Psychopharmacology (Berl), 118*(2), 171-7.

Wills, T. A. & Shiffman, P. (1985). Coping and substance use: a conceptual framework. In *Coping and substance use* (eds. S. Shiffman & T. Wills). Orlando Academic Press: Orlando.

Windle, M., & Windle, R. C. (2001). Depressive symptoms and cigarette smoking among middle adolescents: prospective associations and intrapersonal and interpersonal influences. *J Consult Clin Psychol, 69*(2), 215-26.

Wingard, D. L., Berkman, L. F., & Brand, R. J. (1982). A multivariate analysis of health-related practices: a nine-year mortality follow-up of the Alameda County Study. *Am J Epidemiol, 116*(5), 765-75.

Wise, R. A., & Rompre, P. P. (1989). Brain dopamine and reward. *Annu Rev Psychol, 40*, 191-225.

Wonnacott, S. (1990). Characterization of brain nicotinic receptor sites. In *Nicotine pharmacology: molecular, cellular and behavioural aspects* (eds. S. Wonnacott, M. Russell, I. Stolerman), 226-77. Oxford University Press: Oxford.

Wonnacott, S., Drasdo, A., Sanderson, E., & Rowell, P. (1990). Presynaptic nicotinic receptors and the modulation of transmitter release. *Ciba Found Symp, 152*, 87-101.

Wonnacott, S., Irons, J., Rapier, C., Thorne, B., & Lunt, G. G. (1989). Presynaptic modulation of transmitter release by nicotinic receptors. *Prog Brain Res, 79*, 157-63.

Woody, G. E., Cottler, L. B., & Cacciola, J. (1993). Severity of dependence - data from the DSM-IV field trials. *Addiction, 88*(11), 1573-79.

World Health Organisation (1998). *International Statistical Classification of Diseases and related Health Problems,* 10th Revision. WHO: Geneva.

Wu, X., Hudmon, K. S., Detry, M. A., Chamberlain, R. M., & Spitz, M. R. (2000). D2 dopamine receptor gene polymorphisms among African-Americans and Mexican-Americans: a lung cancer case-control study. *Cancer Epidemiol Biomarkers Prev, 9*(10), 1021-6.

Yoshida, K., Hamajima, N., Kozaki, K., Saito, H., Maeno, K., Sugiura, T., Ookuma, K., & Takahashi, T. (2001). Association between the dopamine D2 receptor A2/A2 genotype and smoking behavior in the Japanese. *Cancer Epidemiol Biomarkers Prev, 10*(4), 403-5.

Zhu, S. H., Stretch, V., Balabanis, M., Rosbrook, B., Sadler, G., & Pierce, J. P. (1996). Telephone counseling for smoking cessation: effects of single-session and multiple-session interventions. *J Consult Clin Psychol, 64*(1), 202-11.

Zinberg, N. E., & Jacobson, R. C. (1976). The natural history of "chipping". *Am J Psychiatry, 133*(1), 37-40.

Zinser, M. C., Baker, T. B., Sherman, J. E., & Cannon, D. S. (1992). Relation between self-reported affect and drug urges and cravings in continuing and withdrawing smokers. *J Abnorm Psychol, 101*(4), 617-29.

Zoli, M., Lena, C., Picciotto, M. R., & Changeux, J. P. (1998). Identification of four classes of brain nicotinic receptors using beta2 mutant mice. *J Neurosci, 18*(12), 4461-72.

Zoli, M., Picciotto, M. R., Ferrari, R., Cocchi, D., & Changeux, J. P. (1999). Increased neurodegeneration during ageing in mice lacking high-affinity nicotine receptors. *EMBO J, 18*(5), 1235-44.

Zuckerman, M. (1971). Dimensions of sensation seeking. *J Consult Clin Psych, 36*(1), 45-52.

Zuckerman, M. (1990). The psychophysiology of sensation seeking. *J Pers, 58*(1), 313-45.

Zuckerman, M., Ball, S., & Black, J. (1990). Influences of sensation seeking, gender, risk appraisal, and situational motivation on smoking. *Addict Behav, 15*(3), 209-20.

APPENDICES

I. Reasons for Smoking Questionnaire (RFS)

RFS

Please read the following statements and indicate your response by ticking one of the boxes to the right of the sentence.

(1=never, 2=seldom, 3=occasionally, 4=frequently, 5=always)

1 2 3 4 5

I smoke cigarettes to stimulate me, to perk myself up_____

I've found a cigarette in my mouth and didn't remember putting it there_____

When I am trying to solve a problem, I light up a cigarette_

When I smoke a cigarette, part of the enjoyment is watching the smoke as I exhale it_____

I am very much aware of the fact when I am not smoking a cigarette_____

Part of the enjoyment of smoking a cigarette comes from the steps I take to light up_____

When I feel "blue" or want to take my mind off cares and worries, I smoke cigarettes_____

I smoke cigarettes automatically without even being aware of it_____

I smoke cigarettes in order to keep from slowing down ___

I get a real gnawing hunger for a cigarette when I haven't smoked for a while_____

When I feel uncomfortable or upset about something, I light up a cigarette_____

Handling a cigarette is part of the enjoyment of smoking it_

Between cigarettes, I get a craving that *only* a cigarette can satisfy_____

I light up a cigarette when I feel angry about something___

(1=never, 2=seldom, 3=occasionally, 4=frequently, 5=always)

	1	2	3	4	5
I light up a cigarette without realising I still have one burning in the ash-tray					
I find cigarettes pleasurable					
When I feel ashamed or embarrassed about something, I light up a cigarette					
When I have run out of cigarettes I find it almost unbearable until I can get them					
Few things help better than cigarettes when I'm feeling upset					
I smoke cigarettes just from habit, without even really wanting the one I'm smoking					
Smoking cigarettes is pleasant and relaxing					
I do not feel contented for long unless I am smoking a cigarette					
I smoke cigarettes to give me a "lift"					

II. Smoking Motivation Questionnaire (SMQ)

SMQ

This questionnaire asks you to consider the various motives you might have for smoking. It asks you to think about different aspects of smoking, and rate them on how and when they apply to your individual smoking habits. Please tick one box for each item indicating your response.

(0=not at all, 1=a little, 2=quite a bit, 3=very much so)

	0	1	2	3
I smoke in order to keep myself from slowing down				
Handling a cigarette is part of the enjoyment of smoking it				
I smoke for the pleasure of having something to put in my mouth				
I want to smoke most when I am comfortable and relaxed				
Part of the enjoyment of smoking is watching the smoke as I blow it out				
I smoke more when I am worried about something				
I like smoking while I am busy and working hard				
I smoke for the pleasure of offering and accepting cigarettes from other people				
When I run out of cigarettes I find it almost unbearable until I can get them				
I smoke automatically without even being aware of it				
I feel I look more mature and sophisticated when smoking				
Smoking helps me keep going when I'm tired				
Part of the enjoyment of smoking comes from the steps I take to light it up				
One reason I smoke is because it tastes so good				

(0=not at all, 1=a little, 2=quite a bit, 3=very much so)

	0	1	2	3
After meals is the time I most enjoy smoking				
Smoking helps me to think and concentrate				
I am very much aware of the fact when I am not smoking				
It is easier to talk and get on with other people when smoking				
I light up a cigarette without realising I still have one burning in the ashtray				
Smoking cheers me up				
I like a cigarette best when I am having a quiet rest				
While smoking I feel more confident with other people				
I get a definite lift and feel more alert when smoking				
Without a cigarette I don't know what to do with my hands				
I only really enjoy smoking with a drink				
I smoke much more when I am with other people				
I smoke because I like the smell so much				
I usually only smoke when I can sit back and really enjoy it				
I light up a cigarette when I feel angry about something				
I find it a pleasure drawing the smoke into my lungs				
I get a real gnawing hunger to smoke when I haven't smoked for a while				

(0=not at all, 1=a little, 2=quite a bit, 3=very much so)

	0	1	2	3
I find myself smoking without remembering lighting up				
I smoke more when I am rushed and have lots to do				
I feel more attractive to the opposite sex when smoking				

III. Fagerstrom Tolerance Questionnaire (FTQ)

FTQ

Please answer the following questions as honestly as you possibly can. They are trying to establish how much smoking or nicotine has become integrated into your life. Please circle where appropriate, or write a short answer. Thank you.

1. How many cigarettes a day do you smoke?_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

2. What brand do you smoke?_ _

3. Do you inhale? Always / Sometimes / Never

4. Do you smoke more during the morning than during the rest of the day? Yes / No / Depends

5. How soon after you wake up do you smoke your first cigarette?_ _ _ _ _ _ _ _ _ _ _ _hours_ _ _ _ _ _ _ _ _minutes

6. If you had to give up *one* of your daily cigarettes, which cigarette would you hate to give up?_ _

_ _

_ _

_ _

7. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g. in libraries, cinemas, restaurants, religious buildings, etc.? Yes / No / Depends

8. Do you smoke if you are so ill that you are in bed most of the day? Yes / No / Depends

IV. Smoking Beliefs Inventory (SBI)

SBI

This questionnaire asks you about some of the beliefs you might have about smoking. Think about the questions, and try to answer them according to what you yourself believe, rather than what you think the general consensus is.

(0=strongly disagree, 1=slightly disagree, 2=undecided, 3=slightly agree, 4=strongly agree)

0 1 2 3 4

Smoking can help people relax_____

Smoking is a dirty habit_____

Smoking can help people when they feel nervous or embarrassed_____

Smoking improves concentration_____

Smoking does more harm than good_____

Smoking improves memory_____

Children should be discouraged from smoking_____

Smoking is a nuisance_____

Smoking is pleasurable_____

Smoking can kill_____

V. Visual Analogue Mood Scales

Visual analogue mood scales

Subjective mood is assessed using 18 computerised visual analogue mood scales. Each of the 18 bipolar scales are composed of a pair of adjectives, e.g. "drowsy – alert" or "happy – sad". Participants are required to move the cursor (using the response keys with arrows marked left and right) from a central position on the scale anywhere along the horizontal rule, towards either extreme of the scale, until the cursor rests at a position which is representative of their mood state at that exact time. The 18 scales are presented consecutively and always in the same order. The scales are as follows:

1.	Drowsy	v	Alert
2.	Relaxed	v	Excited
3.	Strong	v	Feeble
4.	Muzzy	v	Clear-headed
5.	Co-ordinated	v	Clumsy
6.	Lethargic	v	Energetic
7.	Contented	v	Discontented
8.	Troubled	v	Tranquil
9.	Mentally slow	v	Quick-witted
10.	Tense	v	Calm
11.	Attentive	v	Dreamy
12.	Incompetent	v	Proficient
13.	Happy	v	Sad
14.	Antagonistic	v	Friendly
15.	Interested	v	Bored
16.	Withdrawn	v	Sociable
17.	Depressed	v	Elated
18.	Self-centred	v	Outward-going

For each of these scales a score is recorded between 1 and 51. Using a factor analysis three scores are derived from the 18 scales; alertness, sociability and anxiety. These are derived as follows:

Factor 1 (Alertness)

Scores for measures of feeble, dreamy and clumsy were reversed and then entered into the following equation with the 5 other items loading onto this factor.

Drowsy + muzzy + feeble + clumsy + lethargic + mentally slow + dreamy + incompetent = Factor 1

Factor 2 (Hedonic Tone)

Scores for measures of sad, bored and discontented were reversed and then entered into the following equation with the 3 other items loading onto this factor.

Discontented + sad + antagonistic + bored + withdrawn + self-centred = Factor 2

Factor 3 (Anxiety)

Scores for the measure of excited were reversed and then entered into the following equation with the 2 other items loading on this factor.

Excited + troubled + tense = Factor 3

VI. Simple Reaction Time Task

Simple reaction time task

In this task a frame of a box is displayed in the centre of the screen and at varying temporal intervals (1 – 8 seconds) a target square appears inside the box. As soon as the participant detects the square, they are required to press the response key marked SPACE using the forefinger of their dominant hand only.

- A reaction time is measured for each presentation. A mean reaction time is calculated for each minute of performance on the basis of the number of trials completed per minute.
- The total number of trials completed over the duration of the task is recorded.
- An overall mean reaction time is calculated from the total number of trials completed over the duration of the task.

Analysing raw data using the appropriate data concatenation computer program eliminates any reaction times that are below 200ms and greater than 750ms, in doing so the number of trials completed is reduced correspondingly, i.e. if 1 trial has a reaction time of 760ms that trial will be eliminated from further analysis and will reduce the total number of trials by 1.

Global analysis (measuring general speed of response):

1. Total number of trials completed over the duration of the task.
2. Total mean reaction time calculated across the duration of the test period.

Further analysis:

1. Reaction times for each minute can be looked at separately to observe time on task changes.
2. A fatigue measures can be calculated by subtracting mean reaction time at 1 minute from the mean reaction time at the final minute. A positive fatigue score indicates that reaction times increase as the test progresses as a result of fatigue.

VII. Focused Attention Task

Focused attention task

In this task target letters appear in upper case 'A's and 'B's in the centre of the screen. Participants are required to respond to the target letter presented in the centre of the screen, ignoring any distracters presented in the periphery, as quickly and as accurately as possible. The correct response to 'A' is to press the far left response key with the forefinger of the left hand, while the correct response to 'B' is to press the far right key with the forefinger of the right hand. Prior to each target presentation, three warning crosses are presented on the screen. These crosses appear for 500ms and are then replaced by the target letter. The central (target) letter is either accompanied by 1) nothing, 2) asterisks, 3) letters that are the same as the target or 4) letters that are different to the target. The two distracters if and when presented are always identical and the targets and distracter letters are always A or B.

Participants are presented with ten practice trials followed by 4 blocks of 64 trials. In each block there are equal numbers of near / far conditions (warning crosses and, if present, distracters either close or further away from target), 'A' and 'B' target presentations and equal numbers of the four distracter conditions. The condition of the trial order is also controlled.

Preliminary analysis

Raw data for this task provides a reaction time for each presentation and whether or not an accurate response was given. Additionally, number of correct responses with a reaction time less than 800ms, number of correct responses with reaction time greater than 800ms and overall number of errors made are also recorded in the raw data. The concatenation program creates several derived variables measuring different aspects of selective attention using the raw data.

These variables include:

- Mean reaction time responding to targets presented alone or with asterisks.
- Mean reaction time when distracters are present, whether they agree/disagree.
- Speed of encoding of information - the difference in reaction time of response between conditions when the target is alternated from the previous trial and when the target is repeated from the previous trial.
- The Eriksen effect - a measure of the focusing of attention - the difference in reaction time between responses with distracters near to the target and responses with distracters far from the target. If attention is focused then a big difference between near and far distracter conditions should be found. If attention is set at a wide angle then this difference should be reduced.
- Mean reaction time when target is presented alone.
- Mean accuracy responding to the target when presented alone or with asterisks (divide by number of blocks of 64 and multiply by 100 to calculate percentage).
- Mean accuracy when distracters are present, whether they are agreeing (same letters as target) or disagreeing (different letters to target) or asterisks (divide by number of blocks of 64 and multiply by 100 to calculate percentage).
- Number of long responses (reaction times >800ms).
- Number of errors.

VIII. Categoric Search Task

Categoric search task

This task is similar to the focused attention task. Each trial begins with the appearance of two crosses either in the central positions occupied by the non-targets in the focused attention task or further apart, located towards either the left or right extremes of the screen. The target letter then appears in place of one of these crosses, however in this task the left/right location is unknown. On half the trials the target letter 'A' or 'B' is presented alone and on the other half it is accompanied by a distracter (a digit between 1 and 7). As with the focused attention task, the number of near/far stimuli, 'A' versus 'B' targets and distracter/no distracter conditions are controlled. Half of the trials lead to compatible responses (i.e. the letter 'A' on the left side of the screen, or letter 'B' on the right: this means visual stimulus and correct motor response are on the same side) whereas the others are incompatible. The nature of the preceding trial is also controlled. In other respects (practice trials, blocks, number of trials, etc.) the task is identical to the focused attention task.

Preliminary analysis

The raw data provides a reaction time for each presentation and records whether or not an accurate response was given. In addition, the number of correct responses with a reaction time less than 1000ms, the number of correct responses with reaction time greater than 1000ms and the overall number of errors made are also recorded in the raw data. The concatenation program also uses the raw data and derives several scores measuring different aspects of selective attention.

For the categoric search task the variables include:

- Mean reaction time when target is presented alone.
- Speed of encoding of information – the difference in reaction time of response between conditions when the target is alternated from the previous trial and when the target is repeated from the previous trial.
- The effect of spatial uncertainty on mean reaction time – difference in reaction time between far and near targets in blank and compatible conditions.
- The effect of compatibility of the target position and the response key on reaction time – the difference in reaction times between incompatible and compatible presentations.
- The effect of target location – the difference in reaction time between responses to targets presented in different locations and targets presented in the same locations.
- Mean reaction time in blank, near and compatible conditions.
- Mean accuracy when target is presented alone or with asterisk (divide by number of blocks of 64 and multiply by 100 to calculate percentage).
- Number of long responses (>1000ms).
- Number of errors.

The focused attention and categoric search tasks are sophisticated in their ability to measure a number of aspects of selective attention, whilst the participant requires no change in test strategy or level of difficulty. The aim of the various derived scores is to examine the effects of various distracting stimuli in relation to the target letter, upon

reaction time and accuracy of response and therefore their effects upon attentional processes.

Design specifications for focused attention and categoric search tasks
'Near' and 'Far' refer to presentations of the target letter near the center of the screen or at the extreme edges of the screen (i.e. far from the centre). These are programmed as either 2 character spaces from the centre, left and right (NEAR condition); or 34 character spaces from the centre, left and right (FAR condition).

The font size of the characters presented is NORMAL character set for a DOS screen operating in 320x480 video mode.

Reaction times <100ms are excluded during the concatenation process. Long responses are specified in the concatenation program (>800ms in focused attention; >1000ms in categoric search). The inter-stimulus time (i.e. time between presentation of warning crosses and target letter) is set at 120ms.

IX. Psychomotor (5-Choice) Task

Five-choice psychomotor task

This task is a measure of both speed and accuracy of movement to a choice of targets. Five buttons are arranged on the response box in a regular pentagon with a sixth button in the centre. A light appears in one of the peripheral buttons. The participant is required to extinguish the illuminated button simply by pressing it using the forefinger of the dominant hand only. Following this the centre key will illuminate. The participant is required to press the central light and continue to follow the light around the board in this periphery button, central button, periphery button sequence.

For each minute of the task and over the duration of the task the following measures are recorded:

- Total number of trials completed
- Total percentage of trials performed correctly
- Total number of long responses (reaction times >1500ms)

Global analysis

1. Total number of trials completed within the duration of the task.
2. Total percentage of trials performed correctly within the duration of the task.
3. Total number of long responses (reaction times >1500ms) within the duration of the task.

Further analysis

Number of trials completed in each minute of the task (can be used to observe changes in rate of task performance within task duration).

Percentage of correct trials in each minute of the task (can be used to observe changes in accuracy of task performance within task duration).

Number of long responses made in each minute of the task (can be used to observe changes in frequency of attentional lapses within task duration).

X. Rapid Visual Information Processing (RVIP)/Vigilance Task

Rapid visual information processing/vigilance repeated digits detection task

This visual cognitive vigilance task measures the ability to detect targets at irregular intervals. Participants are shown successive presentations of three-digit numbers in the centre of the screen (e.g. 473) at the rate of 100 per minute. Each three-digit number usually differs from the one preceding it, with one of the three digits being replaced with a different digit (e.g. 463, 563, 562). Occasionally (8 times per minute) the same three-digit number will be presented on successive trials. It is these repetitions that the participant needs to detect and respond to as quickly as possible by pressing the space key on the keyboard using the forefinger of the dominant hand.

For each minute of the task and over the whole duration of the task the following measures are recorded:

- Total mean reaction time to targets
- Total percentage of targets correctly detected
- Total number of false alarms

Global analysis

1. Total mean reaction time calculated over the entire test period.
2. Total hit rate is calculated by adding the number of hits for each trial period.
3. Total false alarm rate is calculated by adding the number of false alarms for each trial period.

Further analysis

1. Reaction times for each of the trial periods can be looked at separately to observe changes throughout the duration of the test.
2. Hit rates for each of the trial periods can be looked at separately to observe changes in accuracy throughout the duration of the test.
3. A fatigue measure can be calculated by subtracting mean reaction time at trial period 1 from the mean reaction time at the final trial period. A positive fatigue score indicates that reaction times increase as the test progresses as a result of fatigue.
4. A second fatigue measure can be calculated by subtracting hit rate for trial period 1 from the hit rate for the final trial period. If the hit rate difference is found to be negative this also indicates that vigilance is being reduced by the effect of fatigue over the duration of the test.

XI. Temperament and Character Inventory (TCI)

TEMPERAMENT AND CHARACTER INVENTORY

SMOKING STUDY 1999

NAME_____

SUBJECT NO._____

Version 9 – Revised 10-26-92

T C I

In this booklet you will find statements people might use to describe their attitudes, opinions, interests, and other personal feelings.

Each statement can be answered TRUE or FALSE. Read the statement and decide which choice best describes you. Try to describe the way you USUALLY or generally act or feel, not just how you are feeling right now.

We would like you to fill out this questionnaire on your own using a pencil. When you are finished, please return the questionnaire.

HOW TO FILL OUT THIS QUESTIONNAIRE

To answer you only need to circle either "T" or "F" after each question. Here is an example:

EXAMPLE	TRUE	FALSE
I understand how to fill out this questionnaire.....	T	F

(If you understand how to fill out this questionnaire, circle "T" to show that the statement is true).

****

Read each statement carefully, but don't spend too much time on deciding the answer.

Please answer every statement, even if you are not completely sure of the answer.

Remember there are no right or wrong answers – just describe your own personal opinions and feelings.

Print your Name:_____Age_____D.O.B._____

Black_____White_____Hispanic_____Other_____ SEX: M F

Occupation_____Date_____

1. I often try new things just for fun or thrills,
even if most people think it is a waste of time..... T F

2. I usually am confident that everything will go well,
even in situations that worry most people. ..... T F

3. I am often moved deeply by a fine speech or
poetry. ..... T F

4. I often feel that I am the victim of
circumstances. ..... T F

5. I can usually accept other people as they are,
even when they are very different from me. ..... T F

6. I believe that miracles happen. ..... T F

7. I enjoy getting revenge on people who hurt me..... T F

8. Often when I am concentrating on something, I lose
awareness of the passage of time. ..... T F

9. Often I feel that my life has little purpose
or meaning. ..... T F

10. I like to help find a solution to problems so
that everyone comes out ahead. ..... T F

11. I could probably accomplish more than I do,
but I don't see the point in pushing myself
harder than is necessary to get by. ..... T F

12. I often feel tense and worried in unfamiliar
situations, even when others feel there is
little to worry about. ..... T F

13. I often do things based on how I feel at the
moment without thinking about how they were
done in the past. ..... T F

14. I usually do things my own way -- rather
than giving in to the wishes of other people. ..... T F

15. I often feel so connected to the people around
me that it is like there is no separation
between us. ..... T F

16. I generally don't like people who have different
ideas from me. ..... T F

17. In most situations my natural responses are based
on good habits that I have developed. ..... T F

18. I would do almost anything legal in order to become rich and famous, even if I would lose the trust of many old friends. ..... T F

19. I am much more reserved and controlled than most people. ..... T F

20. I often have to stop what I am doing because I start worrying about what might go wrong. ..... T F

21. I like to discuss my experiences and feelings openly with friends instead of keeping them to myself. ..... T F

22. I have less energy and get tired more quickly than most people. ..... T F

23. I am often called "absent-minded" because I get so wrapped up in what I am doing that I lose track of everything else. ..... T F

24. I seldom feel free to choose what I want to do..... T F

25. I often consider another person's feelings as much as my own. ..... T F

26. Most of the time I would prefer to do something a little risky (like riding in a automobile over steep hills and sharp turns) -- rather than having to stay quiet and inactive for a few hours. ..... T F

27. I often avoid meeting strangers because I lack confidence with people I do not know. ..... T F

28. I like to please other people as much as I can. ..... T F

29. I like old "tried and true" ways of doing things much better than trying "new and improved" ways..... T F

30. Usually I am not able to do things according to their priority of importance to me because of lack of time. ..... T F

31. I often do things to help protect animals and plants from extinction. ..... T F

32. I often wish that I was smarter than everyone else. ..... T F

33. It gives me pleasure to see my enemies suffer. ..... T F

34. I like to be very organized and set up rules for people whenever I can..... T F

35. It is difficult for me to keep the same interests for a long time because my attention often shifts to something else. ..... T F

36. Repeated practice has given me good habits that are stronger than most momentary impulses or persuasion. ..... T F

37. I am usually so determined that I continue to work long after other people have given up. ..... T F

38. I am fascinated by the many things in life that cannot be scientifically explained. ..... T F

39. I have many bad habits that I wish I could break. ..... T F

40. I often wait for someone else to provide a solution to my problems. ..... T F

41. I often spend money until I run out of cash or get into debt from using too much credit. ..... T F

42. I think I will have very good luck in the future. ..... T F

43. I recover more slowly than most people from minor illnesses or stress. ..... T F

44. It wouldn't bother me to be alone all the time. ..... T F

45. Often I have unexpected flashes of insight or understanding while relaxing. ..... T F

46. I don't care very much whether other people like me or the way I do things. ..... T F

47. I usually try to get just what I want for myself because it is not possible to satisfy everyone anyway. ..... T F

48. I have no patience with people who don't accept my views. ..... T F

49. I don't seem to understand most people very well. ..... T F

50. You don't have to be dishonest to succeed in business. ..... T F

51. I sometimes feel so connected to nature that everything seems to be part of one living organism. ..... T F

52. In conversations I am much better as a listener than as a talker. ..... T F

53. I lose my temper more quickly than most people. ..... T F

54. When I have to meet a group of strangers, I am more shy than most people. ..... T F

55. I am more sentimental than most people. ..... T F

56. I seem to have a "sixth sense" that sometimes allows me to know what is going to happen. ..... T F

57. When someone hurts me in any way, I usually try to get even. ..... T F

58. My attitudes are determined largely by influences outside my control. ..... T F

59. Each day I try to take another step toward my goals. ..... T F

60. I often wish I was stronger than everyone else. ..... T F

61. I like to think about things for a long time before I make a decision. ..... T F

62. I am more hard-working than most people. ..... T F

63. I often need naps or extra rest periods because I get tired so easily. ..... T F

64. I like to be of service to others. ..... T F

65. Regardless of any temporary problem that I have to overcome, I always think it will turn out well. ..... T F

66. It is hard for me to enjoy spending money on myself, even when I have saved plenty of money. ..... T F

67. I usually stay calm and secure in situations that most people would find physically dangerous. ..... T F

68. I like to keep my problems to myself. ..... T F

69. I don't mind discussing my personal problems with people whom I have known briefly or slightly. ..... T F

70. I like to stay at home better than to travel or explore new places. ..... T F

71. I do not think it is smart to help weak people who cannot help themselves. ..... T F

72. I cannot have any peace of mind if I treat other people unfairly, even if they are unfair to me. ..... T F

73. People will usually tell me how they feel. ..... T F

74. I often wish I could stay young forever. ..... T F

75. I am usually more upset than most people by the loss of a close friend. ..... T F

76. Sometimes I have felt like I was part of something with no limits or boundaries in time and space. ..... T F

77. I sometimes feel a spiritual connection to other people that I cannot explain in words. ..... T F

78. I try to be considerate of other people's feelings, even when they have been unfair to me in the past. ..... T F

79. I like it when people can do whatever they want without strict rules and regulations. ..... T F

80. I would probably stay relaxed and outgoing when meeting a group of strangers, even if I were told they are unfriendly. ..... T F

81. Usually I am more worried than most people that something might go wrong in the future. ..... T F

82. I usually think about all the facts in detail before I make a decision. ..... T F

83. I feel it is more important to be sympathetic and understanding of other people than to be practical and tough-minded. ..... T F

84. I often feel a strong sense of unity with all the things around me. ..... T F

85. I often wish I had special powers like Superman. ..... T F

86. Other people control me too much. ..... T F

87. I like to share what I have learned with other people. ..... T F

88. Religious experiences have helped me understand the real purpose of my life. ..... T F

89. I often learn a lot from people. ..... T F

90. Repeated practice has allowed me to become good at many things that help me to be successful. ..... T F

91. I am usually able to get other people to believe me, even when I know that what I am saying is exaggerated or untrue. ..... T F

92. I need much extra rest, support, or reassurance to recover from minor illnesses or stress. ..... T F

93. I know there are principles for living that no one can violate without suffering in the long run. ..... T F

94. I don't want to be richer than everyone else. ..... T F

95. I would gladly risk my own life to make the world a better place. ..... T F

96. Even after thinking about something a long time, I have learned to trust my feelings more than my logical reasons. ..... T F

97. Sometimes I have felt my life was being directed by a spiritual force greater than any human being. ..... T F

98. I usually enjoy being mean to anyone who has been mean to me. ..... T F

99. I have a reputation as someone who is very practical and does not act on emotion. ..... T F

100. It is easy for me to organize my thoughts while talking to someone. ..... T F

101. I often react so strongly to unexpected news that I say or do things that I regret. ..... T F

102. I am strongly moved by sentimental appeals (like when asked to help crippled children). ..... T F

103. I usually push myself harder than most people do because I want to do as well as I possibly can. ..... T F

104. I have so many faults that I don't like myself very much. ..... T F

105. I have too little time to look for long-term solutions for my problems. ..... T F

106. I often cannot deal with problems because I just don't know what to do. ..... T F

107. I often wish I could stop the passage of time. ..... T F

108. I hate to make decisions based only on my first impressions. ..... T F

109. I prefer spending money rather than saving it. ..... T F

110. I can usually do a good job of stretching the truth to tell a funnier story or to play a joke on someone. ..... T F

111. Even after there are problems in a friendship, I nearly always try to keep it going anyway. ..... T F

112. If I am embarassed or humiliated, I get over it very quickly. ..... T F

113. It is extremely difficult for me to adjust to changes in my usual way of doing things because I get so tense, tired, or worried. ..... T F

114. I usually demand very good practical reasons before I am willing to change my old ways of doing things. ..... T F

115. I need a lot of help from other people to train me to have good habits. ..... T F

116. I think that extra-sensory perception (ESP, like telepathy or precognition) is really possible. ..... T F

117. I would like to have warm and close friends with me most of the time. ..... T F

118. I often keep trying the same thing over and over again, even when I have not had much success in a long time. ..... T F

119. I nearly always stay relaxed and carefree, even when nearly everyone else is fearful. ..... T F

120. I find sad songs and movies pretty boring. ..... T F

121. Circumstances often force me to do things against my will. ..... T F

122. It is hard for me to tolerate people who are different from me. ..... T F

123. I think that most things that are called miracles are just chance. ..... T F

124. I would rather be kind than to get revenge when someone hurts me. ..... T F

125. I often become so fascinated with what I'm doing that I get lost in the moment - like I'm detached from time and place. ..... T F

126. I do not think I have a real sense of purpose for my life. ..... T F

127. I try to cooperate with others as much as possible. ..... T F

128. I am satisfied with my accomplishments, and have little desire to do better. ..... T F

129. I often feel tense and worried in unfamiliar situations, even when others feel there is no danger at all. ..... T F

130. I often follow my instincts, hunches, or intuition without thinking through all the details. ..... T F

131. Other people often think that I am too independent because I won't do what they want. ..... T F

132. I often feel a strong spiritual or emotional connection with all the people around me. ..... T F

133. It is usually easy for me to like people who have different values from me. ..... T F

134. I try to do as little work as possible, even when other people expect more of me. ..... T F

135. Good habits have become "second nature" to me -- they are automatic and spontaneous actions nearly all the time. ..... T F

136. I don't mind the fact that other people often know more than I do about something.

137. I usually try to imagine myself "in other people's shoes", so I can really understand them. ..... T F

138. Principles like fairness and honesty have little role in some aspects of my life. ..... T F

139. I am better at saving money than most people. ..... T F

140. I seldom let myself get upset or frustrated: when things don't work out, I simply move on to other activities. ..... T F

141. Even when most people feel it is not important, I often insist on things being done in a strict and orderly way. ..... T F

142. I feel very confident and sure of myself in almost all social situations. ..... T F

143. My friends find it hard to know my feelings because I seldom tell them about my private thoughts. ..... T F

144. I hate to change the way I do things, even if many people tell me there is a new and better way to do it. ..... T F

145. I think it is unwise to believe in things that cannot be explained scientifically. ..... T F

146. I like to imagine my enemies suffering. ..... T F

147. I am more energetic and tire less quickly than most people. ..... T F

148. I like to pay close attention to details in everything I do. ..... T F

149. I often stop what I am doing because I get worried, even when my friends tell me everything will go well. ..... T F

150. I often wish I was more powerful than everyone else. ..... T F

151. I usually am free to choose what I will do. ..... T F

152. Often I become so involved in what I am doing that I forget where I am for a while. ..... T F

153. Members of a team rarely get their fair share. ..... T F

154. Most of the time I would prefer to do something risky (like hang-gliding or parachute jumping) -- rather than having to stay quiet and inactive for a few hours. ..... T F

155. Because I so often spend too much money on impulse, it is hard for me to save money -- even for special plans like a vacation. ..... T F

156. I don't go out of my way to please other people. ..... T F

157. I am not shy with strangers at all. ..... T F

158. I often give in to the wishes of friends. ..... T F

159. I spend most of my time doing things that seem necessary but not really important to me. ..... T F

160. I don't think that religious or ethical principles about what is right and wrong should have much influence in business decisions. ..... T F

161. I often try to put aside my own judgments so that I can better understand what other people are experiencing. ..... T F

162. Many of my habits make it hard for me to accomplish worthwhile goals. ..... T F

163. I have made real personal sacrifices in order to make the world a better place -- like trying to prevent war, poverty and injustice. ..... T F

164. I never worry about terrible things that might happen in the future. ..... T F

165. I almost never get so excited that I lose control of myself. ..... T F

166. I often give up a job if it takes much longer than I thought it would. ..... T F

167. I prefer to start conversations, rather than waiting for others to talk to me. ..... T F

168. Most of the time I quickly forgive anyone who does me wrong. ..... T F

169. My actions are determined largely by influences outside my control. ..... T F

170. I often have to change my decisions because I had a wrong hunch or mistaken first impression. ..... T F

171. I prefer to wait for someone else to take the lead in getting things done. ..... T F

172. I usually respect the opinions of others. ..... T F

173. I have had experiences that made my role in life so clear to me that I felt very excited and happy. ..... T F

174. It is fun for me to buy things for myself. ..... T F

175. I believe that I have experienced extra-sensory perception myself. ..... T F

176. I believe that my brain is not working properly. ..... T F

177. My behavior is strongly guided by certain goals that I have set for my life. ..... T F

178. It is usually foolish to promote the success of other people. ..... T F

179. I often wish I could live forever. ..... T F

180. I usually like to stay cool and detached from other people. ..... T F

181. I am more likely to cry at a sad movie than most people. ..... T F

182. I recover more quickly than most people from minor illnesses or stress. ..... T F

183. I often break rules and regulations when I think I can get away with it. ..... T F

184. I need much more practice in developing good habits before I will be able to trust myself in many tempting situations. ..... T F

185. I wish other people didn't talk as much as they do. ..... T F

186. Everyone should be treated with dignity and respect, even if they seem to be unimportant or bad. ..... T F

187. I like to make quick decisions so I can get on with what has to be done. ..... T F

188. I usually have good luck in whatever I try to do. ..... T F

189. I am usually confident that I can easily do things that most people would consider dangerous (such as driving an automobile fast on a wet or icy road). ..... T F

190. I see no point in continuing to work on something unless there is a good chance of success. ..... T F

191. I like to explore new ways to do things. ..... T F

192. I enjoy saving money more than spending it on entertainment or thrills. ..... T F

193. Individual rights are more important than the needs of any group. ..... T F

194. I have had personal experiences in which I felt in contact with a divine and wonderful spiritual power. ..... T F

195. I have had moments of great joy in which I suddenly had a clear, deep feeling of oneness with all that exists. ..... T F

196. Good habits make it easier for me to do things the way I want. ..... T F

197. Most people seem more resourceful than I am. ..... T F

198. Other people and conditions are often to blame for my problems. ..... T F

199. It gives me pleasure to help others, even if they have treated me badly. ..... T F

200. I often feel like I am a part of the spiritual force on which all life depends. ..... T F

201. Even when I am with friends, I prefer not to "open up" very much. ..... T F

202. I usually can stay "on the go" all day without having to push myself. ..... T F

203. I nearly always think about all the facts in detail before I make a decision, even when other people demand a quick decision. ..... T F

204. I am not very good at talking my way out of trouble when I am caught doing something wrong. ..... T F

205. I am more of a perfectionist than most people. ..... T F

206. Whether something is right or wrong is just a matter of opinion. ..... T F

207. I think my natural responses now are usually consistent with my principles and long-term goals. ..... T F

208. I believe that all life depends on some spiritual order or power that cannot be completely explained. ..... T F

209. I think I would stay confident and relaxed when meeting strangers, even if I were told they are angry at me. ..... T F

210. People find it easy to come to me for help, sympathy, and warm understanding. ..... T F

211. I am slower than most people to get excited about new ideas and activities. ..... T F

212. I have trouble telling a lie, even when it is meant to spare someone else's feelings. ..... T F

213. There are some people I don't like. ..... T F

214. I don't want to be more admired than everyone else. ..... T F

215. Often when I look at an ordinary thing, something wonderful happens -- I get the feeling that I am seeing it fresh for the first time. ..... T F

216. Most people I know look out only for themselves, no matter who else gets hurt. ..... T F

217. I usually feel tense and worried when I have to do something new and unfamiliar. ..... T F

218. I often push myself to the point of exhaustion or try to do more than I really can. ..... T F

219. Some people think I am too stingy or tight with my money. ..... T F

220. Reports of mystical experiences are probably just wishful thinking. ..... T F

221. My will power is too weak to overcome very strong temptations, even if I know I will suffer as a consequence. ..... T F

222. I hate to see anyone suffer. ..... T F

223. I know what I want to do in my life. ..... T F

224. I regularly take time to consider whether what I am doing is right or wrong. ..... T F

225. Things often go wrong for me unless I am very careful. ..... T F

226. If I am feeling upset, I usually feel better around friends than when left alone. ..... T F

227. I don't think it is possible for one person to share feelings with someone else who hasn't had the same experiences. ..... T F

228. It often seems to other people like I am in another world because I am so completely unaware of things going on around me. ..... T F

229. I wish I were better looking than everyone else. ..... T F

230. I have lied a lot on this questionnaire. ..... T F

231. I usually stay away from social situations where I would have to meet strangers, even if I am assured that they will be friendly. ..... T F

232. I love the blooming of flowers in the spring as much as seeing an old friend again. ..... T F

233. I usually look at a difficult situation as a challenge or opportunity. ..... T F

234. People involved with me have to learn how to do things my way. ..... T F

235. Dishonesty only causes problems if you get caught. ..... T F

236. I usually feel much more confident and energetic than most people, even after minor illnesses or stress. ..... T F

237. I like to read everything when I am asked to sign any papers. ..... T F

238. When nothing new is happening, I usually start looking for something that is thrilling or exciting. ..... T F

239. Sometimes I get upset. ..... T F

240. Occasionally I talk about people behind their backs. ..... T F

XII. Genotyping Consent Form

SUBJECT CONSENT FORM

I hereby consent to the use of genetic material obtained from the cheek cell sample I have volunteered being analysed. I understand that *three genotypes only* will be investigated: **DRD2, DRD3** and **DRD4** (all neurotransmitter receptors in the brain) polymorphisms. If at any stage further data is needed from my DNA, I will receive a written request from the University to that end. I am within my rights to withdraw at any time, and may refuse further experimentation at will.

Name:

Subject Number:

Signed:

XIII. Psychosocial Questionnaire Measures

Study:	
Recruitment Number:	
Study Number:	
Date Completed:	

PSYCHOSOCIAL QUESTIONS

Book 1

Your eating habits

INSTRUCTIONS: Please circle the appropriate answer for each question

1. Are you on a special diet of any sort for health reasons?

No (0) **Yes (1)**

If yes: What are the reasons?
What is the special diet?

2. Would you say that you usually eat the right amount of food for you?

No (0) Yes (1)

2.a If no: Do you eat too much or too little?
1 = too much 2 = too little

3. How often do you eat breakfast ?

Every day	Most days (3-6)	Once or twice a week	Less than once a week	Never
(4)	(3)	(2)	(1)	(0)

4. Apart from breakfast, how many main or cooked meals (i.e. a meal that has a main course with one or more vegetables) do you usually have during the day? _____

5. Apart from breakfast, how many lighter meals do you usually have during the day?_____

6. How often do you have a snack or something to eat between meals or before going to bed?

Every day	Most days (3-6)	Once or twice a week	Less than once a week	Never
(4)	(3)	(2)	(1)	(0)

6.a If every day: How often ?

1= once or twice 2 = 3 or 4 3 = 4+

7. Do you eat regularly; i.e. have the same number of meals and snacks at roughly the same time each day?

No (0) Yes (1)

8. How often do you eat fried foods (don't count chips)?

Every day	Most days (3-6)	Once or twice a week	less than once a week	Never
(4)	(3)	(2)	(1)	(0)

9a. How many cups of caffeinated coffee do you usually drink in a day?

1 or 2	3 or 4	5 or 6	6+	None
(1)	(3)	(5)	(6)	(0)

9b. How many cups of tea do you usually drink in a day?

1 or 2	3 or 4	5 or 6	6+	None
(1)	(3)	(5)	(6)	(0)

10. There will now follow a list of foods. Please indicate, by circling the appropriate answer, how often you eat each of them.

		More than once a day	Once a day	Most days (3-6)	Once or twice a week	Less than once a week	Never
A	Fresh fruit	6	5	4	3	2	1
B	Salads or raw veg.	6	5	4	3	2	1
C	Tinned fruit	6	5	4	3	2	1
D	Chips	6	5	4	3	2	1
E	Potatoes (**NOT CHIPS**)	6	5	4	3	2	1
F	Root vegetables like carrots, turnips and parsnips	6	5	4	3	2	1
G	Peas and beans (all kinds)	6	5	4	3	2	1
H	Green vegetables	6	5	4	3	2	1
I	Other cooked vegetables, inc. mushrooms and onions	6	5	4	3	2	1
J	Nuts	6	5	4	3	2	1

K	Potato crisps/similar snacks	6	5	4	3	2	1
		More than once a day	Once a day	Most days (3-6)	Once or twice a week	Less than once a week	Never
L	Sweets, chocolates	6	5	4	3	2	1
M	Pasta and rice	6	5	4	3	2	1
N	Breakfast cereal	6	5	4	3	2	1
O	Biscuits	6	5	4	3	2	1
P	Cakes of all kinds	6	5	4	3	2	1
Q	Sweets or puddings, fruit pies, and flans and tarts	6	5	4	3	2	1
R	Ice cream, mousse, yoghurt, milk puddings	6	5	4	3	2	1
S	Soft drinks; e.g. colas	6	5	4	3	2	1
T	Pure fruit juice	6	5	4	3	2	1
U	Jam/Marmalade/Honey	6	5	4	3	2	1
V	Cheese	6	5	4	3	2	1
W	Eggs	6	5	4	3	2	1
X	Cream	6	5	4	3	2	1
Y	Fish	6	5	4	3	2	1
Z	Poultry	6	5	4	3	2	1
	Sausages/Tinned meat/ Pâté, meat pies/pasties, etc.	6	5	4	3	2	1
	Beef/lamb/pork/ham/ bacon	6	5	4	3	2	1

Can you think of any other sorts of food which you eat regularly? (Specify)

a. _____	6	5	4	3	2	1
b. _____	6	5	4	3	2	1

c. _____	6	5	4	3	2	1
d. _____	6	5	4	3	2	1

The following questions are about your <u>drinking habits</u>.

11. Would you say that you are:

0 = a non drinker
1 = a very occasional drinker
2 = an occasional drinker
3 = a regular drinker

12. Would you say that you are:

0 = a light drinker

1 = a moderate drinker
2 = a heavy drinker

13. On how many days have you had an alcoholic drink in the last week?

0 1 2 3 4 5 6 7

14. We would like to know what you had to drink last week:

Please indicate:

the number of 1/2 pints of beer in the last week .....
the number of spirits in the last week
.....
the number of glasses of wine that you had
.....

15. Was last week's drinking:

0 = reasonably typical of your usual pattern
1= rather less than usual
2= rather more than usual

The following questions are about cigarette smoking.

16. Do you smoke at least one cigarette a day?

No (0) Yes (1)

If yes:
17. On average, how many cigarettes do you smoke each day? _____
(Number of cigarettes; if less than 1 put 1)

The following questions concern activities and exercise.

18. How often do you take walks, runs or jogs in good weather?

0 = never or very infrequently
1 = sometimes
2 = frequently

19. How often do you swim or do aerobic exercise?

0 = never or very infrequently
1 = sometimes
2 = frequently

20. How often do you do physical work around the house or flat?
0 = never or very infrequently
1 = sometimes
2 = frequently

21. How often do you participate in sports like an active ball game (not including sports like golf, bowling, pool or snooker)?
0 = never or very infrequently
1 = sometimes
2 = frequently

22. How often do you take part in sports like golf, bowling or snooker?
0 = never or very infrequently
1 = sometimes
2 = frequently

23. How often do you watch television?
0 = once a week or less
1 = several times
2 = daily, less than two hours
3 = 2 to 4 hours
4 = more than four hours per day

ISEL

INSTRUCTIONS: This scale is made up of a list of statements, each of which may or may not be true about you. For each statement circle 'definitely true' if you are sure it is true about you and 'probably true' if you think it is true but are not absolutely certain. Similarly, you should tick 'definitely false' if you are sure the statement is false and 'probably false' if you think it is false but are not absolutely certain.

1. **There are several people I trust to help solve my problem.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

2. **If I need help mending something, (e.g. an appliance, car, clothes, furniture), there is someone who would help me.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

3. **Most of my friends are more interesting than I am.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

4. **There is someone who takes pride in my accomplishments.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

5. **When I feel lonely, there are several people I can talk to.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

6. **There is no one that I feel comfortable talking to about intimate personal problems.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

7. **I often meet or talk with family or friends.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

8. **Most people I know think highly of me.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

9. **If I need a lift very early in the morning (e.g. to the tube station, train station, or airport), I would have a hard time finding anyone to take me.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

10. **I feel like I'm not always included in my circle of friends.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

11. **There is really no one who can give me an objective view of how I'm handling my problems.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

12. **There are several different people I enjoy spending time with.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

13. **I think that my friends feel that I'm not very good at helping them solve their problems.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

14. **If I were ill and needed someone (friend, family member, or acquaintance) to take me to the doctor, I would have trouble finding someone.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

15. **If I wanted to go on a trip or outing for a day (e.g. to the seaside or countryside), I would have a hard time finding someone to go with me.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

16. **If I needed a place to stay for a week because of an emergency (e.g. water or electricity not working in my flat or house), I could easily find someone who would put me up.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

17. **I feel there is no one I can share my most private worries and fears with.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

18. **If I were ill, I could easily find someone to help me with my daily chores.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

19. **There is someone I can turn to for advice about handling problems with my family.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

20. **I'm as good at doing things as most people are.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

21. **If I decide one afternoon that I would like to go out (e.g. to the cinema) that evening, I could find someone to go with me.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

22. **When I need suggestions on how to deal with a personal problem , I know someone I can turn to.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

23. **If I needed an emergency loan of £100, there is someone (friend, relative or acquaintance) I could get it from.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

24. **In general, people do not have much confidence in me.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

25. **Most people I know do not enjoy the same things that I do.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

26. **There is someone I could turn to for advice about making career plans or about changing my job.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

27. **I don't get invited to do things with others.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

28. **Most of my friends are more successful at making changes in their lives than I am.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

29. **If I had to go away from home for a few weeks, there is someone I know who would look after my house or flat (the plants, pets, garden, etc.).**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

30. **There is really no one I can trust to give me good financial advice.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

31. **If I wanted to have lunch with someone, I could easily find someone to join me.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

32. **I am more satisfied with my life than most people are with theirs.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

33. **If I was stranded 10 miles from home, there is someone I could call who would come and collect me.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

34. **No one I know would throw a birthday party for me.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

35. **It would be difficult to find someone who would lend me their car for a few hours. (If you don't drive, assume for the purpose of this question that you have someone to drive you, but no car).**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

36. **If a family crisis arose, it would be difficult to find someone who could give me good advice about how to handle it.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

37. **I am closer to my friends than most people are to theirs.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

38. **There is at least one person I know whose advice I really trust.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

39. **If I needed some help in moving to a new house or flat, I would have a hard time finding someone to help me.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

40. **I have a hard time keeping pace with my friends.**

4 = definitely true 3 = probably true 2 = probably false 1 = definitely false

INSTRUCTIONS: **Please circle the answer appropriate response.**

1. Marital status:

a. Have you ever been married?

yes (1) no (0)

b. Are you now single, married, separated, divorced, widowed?

single	married	separated	divorced	widowed
(1)	(2)	(3)	(4)	(5)

2. Friends and relatives:

a: How many close friends do you have?

none	1 or 2	3 to 5	6 to 9	10 or more
(0)	(1)	(2)	(3)	(4)

b. How many relatives do you have that you feel close to?

none	1 or 2	3 to 5	6 to 9	10 or more
(0)	(1)	(2)	(3)	(4)

c. How many of these friends do you see at least once a month?

none	1 or 2	3 to 5	6 to 9	10 or more
(0)	(1)	(2)	(3)	(4)

d. How many of these relatives do you see at least once a month?

none	1 or 2	3 to 5	6 to 9	10 or more
(0)	(1)	(2)	(3)	(4)

3. Church and group membership:

Do you belong to any of these types of groups? if so please tick the appropriate box.

a. A social or recreational group?
b. A labour union, commercial group, professional organisation?
c Church group?
d. A group concerned with children (PTA, boy scout)?
e. A group concerned with community betterment, charity or service?

f. Any other group?

Please give details _____

UCLA

INSTRUCTIONS: Please indicate by circling one of the numbers **how often** you feel the way described in each of the statements.

1. How often have you felt in harmony with people around you?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

2. How often do you feel as though you lack companionship?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

3. How often do you feel that there is no one you can turn to?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

4. How often do you feel alone?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

5. How often do you feel part of a group?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

6. How often do you feel that you have a lot in common with the people around you?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

7. How often do you feel that you are no longer close to anyone?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

8. How often do you feel that your interests and ideas are not shared by those around you?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

9. How often do you feel that you are an outgoing person?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

10. How often do you feel that there are people you feel close to?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

11. How often do you feel left out?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

12. How often do you feel that your social relationships are superficial?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

13. How often do you feel that nobody really knows you?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

14. How often do you feel isolated from other people?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

15. How often do you feel that you find companionship when you want it?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

16. How often do you feel that there are people who really understand you?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

17. How often do you feel unhappy because of being so withdrawn?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

18. How often do you feel that people are around you but not with you?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

19. How often do you feel that there are people you can talk to?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

20. How often do you feel that there are people you can turn to?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

INSTRUCTIONS: The next group of questions has to do with your reactions and opinions about a number of situations. We would like to know how much you agree or disagree with each of the statements listed below. Please mark the number which expresses your answer, with numbers 1 and 6 being the extreme answers. We have covered many different points of view. You may find yourself agreeing strongly with some, disagreeing just as strongly with others, and perhaps uncertain about others.

We want to learn about your responses to these situations, so it is important that each response reflects your own feelings.

1. I worry about how well I get along with people.

I agree very much 1 2 3 4 5 6 I disagree very much

2. I often dislike myself.

I agree very much 1 2 3 4 5 6 I disagree very much

3. I often feel very self-conscious.

I agree very much 1 2 3 4 5 6 I disagree very much

4. I often feel inferior to most of the people I know.

I agree very much 1 2 3 4 5 6 I disagree very much

5. I feel confident that some day the people I know will look up to me and respect me.

I agree very much 1 2 3 4 5 6 I disagree very much

6. I feel afraid or anxious when I am going into a room by myself where other people have already gathered and are talking.

I agree very much 1 2 3 4 5 6 I disagree very much

7. I often have the feeling that there is nothing I can do well.

I agree very much 1 2 3 4 5 6 I disagree very much

8. I worry about whether other people like to be with me.

I agree very much 1 2 3 4 5 6 I disagree very much

9. I am often troubled with shyness.

I agree very much 1 2 3 4 5 6 I disagree very much

10. I think that I am a worthless individual.

I agree very much 1 2 3 4 5 6 I disagree very much

11. I am worried that some of my friends may not have a good opinion of me.

I agree very much 1 2 3 4 5 6 I disagree very much

12. I am confident about my abilities.

I agree very much 1 2 3 4 5 6 I disagree very much

13. I sometimes feel so discouraged with myself that I wonder whether anything is worth while.

I agree very much 1 2 3 4 5 6 I disagree very much

14. I feel worried or bothered about what other people think about me.

I agree very much 1 2 3 4 5 6 I disagree very much

SRI

INSTRUCTIONS: The next set of questions has to do with your reactions and opinions about a number of situations. Please indicate by circling the appropriate answer how much you agree or disagree with the statements below. You may find yourself agreeing strongly with some, disagreeing as strongly with others, and perhaps uncertain with others.

We want to learn about your responses to these situations so it is important that your response reflects your feelings.

1. When I get what I want it's usually because I have worked hard for it.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

2. Even when I'm feeling self-confident about most things, I still seem to lack the ability to control social situations.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

3. I have no trouble making and keeping friends.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

4. When I make plans I am almost certain to make them work.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

5. I am not good at guiding the course of a conversation with several others.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

6. I prefer games requiring some luck over games requiring pure skill.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

7. I can learn almost anything if I set my mind to it.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

8. I can usually establish a close personal relationship with someone I find attractive.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

9. My major accomplishments are entirely due to my hard work and skill.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

10. I usually don't set goals because I have a hard time following them through.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

11. When talking with another person, I can usually steer the person toward the topic I want to talk about and away from those I wish to avoid.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

12. Competition discourages excellence.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

13. Often people get ahead just by being lucky.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

14. If I need help in carrying off a plan of mine, it's usually difficult to get others to help.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

15. If there is someone I want to meet, I can usually arrange it.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

16. I often find it hard to get my point of view across to others.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

17. On any sort of competition (for example, an exam, board game, or athletic contest) I like to know how well I do relative to everybody else.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

18. It is pointless to keep working on something that's too difficult for me.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

19. In attempting to smooth over a disagreement, I usually make it worse.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

20. I find it easy to play an important part in most group situations.

I agree very much (5) I mainly agree (4) I slightly agree (3)
I disagree very much (0) I mainly disagree (1) I slightly disagree (2)

LE

INSTRUCTIONS: Below are questions about a number of events that commonly happen in people's lives. Each question is concerned with whether the event has happened to you in the last **12 months**. Please tick **YES** if the event happened and **NO** if it didn't.

If you have responded YES, please indicate whether this was a good or a bad experience by placing a tick in the appropriate column.

		No (0)	**Yes**	**Good** (1)	**Bad** (2)
1.	Have you moved during the last 12 months?	____	____	____	____
2.	Have you broken off an engagement to be married or ended an intimate relationship during the last 12 months?	____	____	____	____
3.	Did you get married during the last 12 months?	____	____	____	____
4.	Did someone close to you die in the last 12 months?	____	____	____	____
5.	Were you separated or divorced during the last 12 months?	____	____	____	____
6.	Did you break up with a close friend during the last 6 months?	____	____	____	____
7.	Has an important relationship (e.g. with a family member or friend) changed during the last 12 months?	____	____	____	____
8.	Have you (or your spouse/ partner) had or adopted a baby during the last 12 months?	____	____	____	____

	No (0)	Yes	Good (1)	Bad (2)
9. Have you or a close friend or family member had a serious accident during the last 12 months?	____	____	____	____
10. Have you or a close friend or family member had a serious illness during the last 12 months?	____	____	____	____
11. Have you (or your spouse/ partner) been pregnant during the last 12 months?	____	____	____	____
12. Have you (or your wife) had an abortion or miscarriage during the last 12 months?	____	____	____	____
13. Have you lost or changed jobs during the last 12 months?	____	____	____	____
14. Have you been involuntarily unemployed during the last 12 months?	____	____	____	____
15. Have you suffered serious financial hardship during the last 12 months?	____	____	____	____
16. Have you had any serious problems or disappointment in work or an educational course during the last 12 months?	____	____	____	____
17. Have you had a significant success in work or an educational course during the last 12 months?	____	____	____	____

		No (0)	Yes	Good (1)	Bad (2)
18.	Has your house been broken into or burgled during the last 12 months?	____	____	____	____
19.	Have you, your wife or other member of your family been assaulted or mugged during the last 12 months?	____	____	____	____
20.	Has the behaviour of any member of your family or close friends been a significant problem for you during the last 12 months?	____	____	____	____
21.	Have you appeared in court during the last 12 months?	____	____	____	____
22.	Have you had a pet die or disappear during the last 12 months?	____	____	____	____
23	Have you (or your spouse/ partner) suffered a significant business or investment loss or had a business you own fail?	____	____	____	____
24.	If there have been other events that you consider to be important during the last 12 months please list the three most significant below and note whether they were good or bad experiences:				
	Event 1:	____	____	____	____
	Event 2:	____	____	____	____
	Event 3:	____	____	____	____

PSS

The questions in this scale ask you about your feelings and thoughts during the **last month**. In each case, please indicate by circling a number how often you felt or thought a certain way.

1. In the last month, how often have you been upset because of something that happened unexpectedly?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

2. In the last month, how often have you felt that you were unable to control the important things in your life?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

3. In the last month, how often have you felt nervous and 'stressed'?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

4. In the last month, how often have you dealt successfully with day to day problems and annoyances?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

5. In the last month, how often have you felt that you were effectively coping with important changes that were occurring in your life?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

6. In the last month, how often have you felt confident about your ability to handle your personal problems?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

7. In the last month, how often have you felt that things were going your way?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

8. In the last month, how often have you felt that you could not cope with all the things that you had to do?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

9. In the last month, how often have you been able to control irritations in your life?

☆ 0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

10. In the last month, how often have you felt that you were on top of things?

☆ 0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

11. In the last month, how often have you been angered because of things that were outside your control?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

12. In the last month, how often have you found yourself thinking about things that you have to accomplish?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

☆ **13. In the last month, how often have you been able to control the way you spend your time?**

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

14. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

☆ = reverse scoring (4-score)

PSS = sum of all.

HPS

INSTRUCTIONS: The items below assess your health-related behaviours. Please answer ALL questions by circling either **'YES'** or **'NO'** to describe your behaviour. Your answer will be kept confidential.

		(1)	(0)
1.	**Have you had your blood pressure read at least once in the past 6 months? (do NOT include readings taken in this unit)**	YES	NO
2.	**Have you visited the dentist for treatment or check-up at least once in the past 6 months?**	YES	NO
3.	**Do you try a lot to avoid eating too much salt?**	YES	NO
4.	**Do you try a lot to avoid eating too much fat?**	YES	NO
5.	**Do you try to eat sufficient fibre in your diet?**	YES	NO
6.	**Do you try to avoid eating too much cholesterol?**	YES	NO
7.	**Do you try to consume enough vitamins and minerals?**	YES	NO
8.	**Do you try to avoid eating too much sugar?**	YES	NO
9.	**Do you try to consume enough calcium?**	YES	NO
10.	**Do you try to keep your weight within the prescribed range for your age?**	YES	NO
11.	**Do you exercise at least three times a week so that you breathe heavily and your pulse is accelerated for at least 20 minutes?**	YES	NO
12.	**Do you smoke?**	YES	NO
13.	**Do you take steps to reduce stress?**	YES	NO
14.	**Do you socialise at least once a week with close friends or relatives?**	YES	NO
15.	**Do you usually sleep from 7 to 8 hours per night?**	YES	NO
16.	**Do you wear a seat belt when in the front seat of a car?**	YES	NO
17.	**Do you have a smoke detector?**	YES	NO

18. **Do you smoke in bed or live with someone who smokes in bed?** YES NO

19. **Do you take special precautions to avoid accidents in the home?** YES NO

HOS

INSTRUCTIONS: The items listed below refer to people's health, both physical and mental. Please read each item carefully and decide to what extent it is characteristic of you. Give each item a rating of how it applies to you by using the following:

1 = Not at all characteristic of me
2 = Slightly characteristic of me
3 = Somewhat characteristic of me
4 = Moderately characteristic of me
5 = Very characteristic of me

Please circle the appropriate number.

NOTE: Remember to respond to all items, even if you are not completely sure. Your answers will be kept in the strictest confidence. Also, please be honest in responding to these statements.

1.	**I am very aware of how healthy I feel**	1	2	3	4	5
2.	**I sometimes wonder what others think of my health**	1	2	3	4	5
3.	**I feel anxious when I think about my health**	1	2	3	4	5
4.	**I feel confident about the condition of my health**	1	2	3	4	5
5.	**I do things that keep me from becoming unhealthy**	1	2	3	4	5
6.	**I'm very motivated to be healthy**	1	2	3	4	5
7.	**I feel like my health is something that I myself am in charge of**	1	2	3	4	5
8.	**My health is determined mostly by chance happenings**	1	2	3	4	5
9.	**I expect that my health will be excellent in the future**	1	2	3	4	5
10.	**I am in good health**	1	2	3	4	5
11.	**I notice immediately when I feel unhealthy**	1	2	3	4	5
12.	**I'm very concerned with how others evaluate my health**	1	2	3	4	5
13.	**I'm worried about my health**	1	2	3	4	5
14.	**I rarely become discouraged about my health**	1	2	3	4	5

15.	**I am motivated to keep myself from becoming unhealthy**	1	2	3	4	5
16.	**I'm strongly motivated to devote time and effort to my health**	1	2	3	4	5
17.	**My health is something I alone am responsible for**	1	2	3	4	5
18.	**The condition of my health is controlled by accidental happenings**	1	2	3	4	5
19.	**I believe that the future of my health will be positive**	1	2	3	4	5
20.	**My health is good**	1	2	3	4	5
21.	**I'm sensitive to internal cues about my health**	1	2	3	4	5
22.	**I'm very aware of what others think of my health**	1	2	3	4	5
23.	**Thinking about my health leaves me with an uneasy feeling**	1	2	3	4	5
24.	**I am pleased with how well and healthy I feel**	1	2	3	4	5
25.	**I try to avoid engaging in behaviours that undermine my health**	1	2	3	4	5
26.	**I have a strong desire to keep myself healthy**	1	2	3	4	5
27.	**My health is determined largely by what I do (and don't do)**	1	2	3	4	5
28.	**Being in good health is just a matter of luck**	1	2	3	4	5
29.	**I do expect to suffer health problems in the future**	1	2	3	4	5
30.	**I am a well exercised person**	1	2	3	4	5
31.	**I know immediately when I'm not in great health**	1	2	3	4	5
32.	**I'm concerned about how my health appears to others**	1	2	3	4	5
33.	**I usually worry about whether I am in good health**	1	2	3	4	5
34.	**I have positive feelings about my health**	1	2	3	4	5

35.	**I really want to prevent myself from being unhealthy**	1	2	3	4	5
36.	**It's really important to me that I keep myself in proper health**	1	2	3	4	5
37.	**What happens to my health is my responsibility**	1	2	3	4	5
38.	**Being healthy has nothing to do with luck**	1	2	3	4	5
39.	**I will probably experience a number of health problems in the future**	1	2	3	4	5
40.	**My health needs a lot of attention to be in excellent condition**	1	2	3	4	5
41.	**I'm very aware of changes in my health**	1	2	3	4	5
42.	**I'm concerned about what other people think of my health**	1	2	3	4	5
43.	**I feel nervous when I think about the state of my health**	1	2	3	4	5
44.	**I feel that I have handled my health very well**	1	2	3	4	5
45.	**I am really motivated to avoid being in bad health**	1	2	3	4	5
46.	**I strive to keep myself in the most healthy condition**	1	2	3	4	5
47.	**Being in good health is a matter of my own ability and effort**	1	2	3	4	5
48.	**I don't believe that chance or luck play a role in my health**	1	2	3	4	5
49.	**I anticipate that my health will deteriorate in the future**	1	2	3	4	5
50.	**My health is in need of attention**	1	2	3	4	5

CFQ

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the last **six months**. Please circle the appropriate number.

		Very often	Quite often	Occa-sionally	Very rarely	Never
1.	Do you read something and fid you haven't been thinking about it and must read it again?	4	3	2	1	0
2.	Do you forget why you went from one part of the house to the other?	4	3	2	1	0
3.	Do you fail to notice signposts on the road?	4	3	2	1	0
4.	Do you find you confuse left and right when giving directions?	4	3	2	1	0
5.	Do you bump into people?	4	3	2	1	0
6.	Do you find that forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
7.	Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8.	Do you say something and realise afterwards that it might be taken as insulting?	4	3	2	1	0
9.	Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10.	Do you lose your temper and regret it?	4	3	2	1	0
11.	Do you leave important letters unanswered for days?	4	3	2	1	0
12.	Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13.	Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0
14.	Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15.	Do you have trouble making your mind up?	4	3	2	1	0
16.	Do you forget appointments?	4	3	2	1	0

	Very often	Quite often	Occa-sionally	Very rarely	Never
17. Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18. Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19. Do you daydream when you ought to be a listening to something?	4	3	2	1	0
20. Do you forget people's names?	4	3	2	1	0
21. Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22. Do you find you can't quite remember something although it's 'on the tip of your tongue'?	4	3	2	1	0
23. Do you find that you forget what you came to the shops to buy?	4	3	2	1	0
24. Do you drop things?	4	3	2	1	0
25. Do you find you can't think of anything to say?	4	3	2	1	0

MHQ

The next few questions ask about the way you personally feel; lots of them may have no application to you at all, but we are asking all kinds of people and want the results for comparison. Please circle the appropriate answer.

During the past six weeks

		(0)	(1)	(2)
1.	Have you felt upset for no reason?	Never	Sometimes	Often
2.	Have you been troubled by dizziness or shortness of breath?	Never	Sometimes	Often
3.	Have you been able to think as quickly as you used to?	Yes	Rather less quickly	Much less quickly
4.	Have you felt as though you might faint?	Never	Sometimes	Often
5.	Have you felt sick or had indigestion?	Never	Sometimes	Often
6.	Have you felt that life is too much effort?	Never	Sometimes	Often
7.	Have you felt uneasy and restless?	Never	Sometimes	Often
8.	Have you found that silly or unreasonable thoughts kept recurring in your mind?	Never	Sometimes	Often
9.	Have you felt tickling or prickling sensations in your body, arms or legs?	Never	Sometimes	Often
10.	Have you regretted much of your past?	No	Moderately	Very much
11.	Have you felt really panicky?	Never	Sometimes	Often
12.	Has your appetite been poor?	No	Moderately poor	Very poor
13.	Have you woken unusually early in the mornings?	Never	Sometimes	Often
14.	Have you felt 'strung up' inside?	Never	Sometimes	Often
15.	Have you had to check things you do to an unnecessary extent?	Never	Sometimes	Often
16.	Have you been able to get off to sleep alright?	Never not	Sometimes not	Often not
17.	Have you had to make a special effort to face up to things (i.e. everyday problems)?	Not more than anyone else	Moderately so	Very much so
18.	Have you had the feeling you are 'going to pieces'?	Never	Sometimes	Often
19.	Has it irritated you if your normal routine was disturbed?	Not at all	A little	Greatly
20.	Have you suffered from excessive sweating or fluttering of the heart?	Never	Sometimes	Often

21.	Have you experienced periods of sadness (more than half a day)?	Never	Sometimes	Often
22.	Have you had dreams which upset you when you woke up?	Never	Sometimes	Often
23.	Have you found yourself worrying about things that do not really matter?	Never	Sometimes	Often
24.	Have you felt unduly tired and exhausted	Never	Sometimes	Often
25.	Have you been able to feel warmth and affection for other people?	Yes	Not much	Very little

In general: (not referring only to the last six weeks)

		Circle the answer which seems to describe how you <u>generally</u> feel or behave.		
		2	1	0
1	Do people say you are too conscientious ?	Often	Sometimes	Never
2	Do you think that "cleanliness is next to godliness" ?	Definitely	To a degree	Not at all
3	Are you a perfectionist ?	Very much so	To a degree	No

CHIPS

Using this scale, we'd like to ask you about some physical symptoms that *people often experience. For* each symptom we would like you to indicate how much that problem has bothered or distressed you during the past month, including today. For each we'd like you to answer by circling 'not at all', 'a little bit', 'moderately', 'quite a bit', or 'extremely'.

In the past 24 hours how often were you bothered by:

1. Dizziness

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

2. Faintness

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

3. Constant fatigue

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

4. Nausea and/or vomiting

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

5. Stomach pains (e.g. cramps)

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

6. Hot or cold spells

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

7. Poor appetite

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

8. Felt weak all over

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

9. Feeling low in energy

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

10. Muscle tension or soreness

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

11. Muscle cramps

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

12. Severe aches and pains

0 = not at all 1 = a little bit 2 = moderately 3 = quite a bit 4 = extremely

Symptom Checklist

1. Please tick the boxes that describe any symptoms you are currently experiencing:

	(Y if ticked, otherwise N)
Physical weakness	☐
Excessive fatigue	☐
Legs feel heavy	☐
Muscle pain in back, arms or legs	☐
Pain in chest	☐
Painful joints	☐
Nausea	☐
Indigestion	☐
Bloated stomach	☐
Wind	☐
Sore throat	☐
Headache	☐
Earache	☐
Sore eyes	☐
Sensitive to noise	☐
Sensitive to light	☐
Feeling hot/cold	☐
Sweating	☐
Shivering	☐
Swollen glands	☐
Racing heart	☐
Insomnia	☐
Depression	☐
Anxiety/panic feelings	☐
Loss of concentration	☐
Loss of memory	☐
Allergies	☐
Other_____	☐

2. What medications are you taking at the moment?

Prescribed drugs: _____

Multivitamins, etc._____

XIV. Withdrawal Symptoms Checklist (WSC)

NAME:_____ SUBJECT NO._____.

WITHDRAWAL SYMPTOMS CHECKLIST

(0=not present, 1=mild, 2=moderate, 3=severe)

	0	1	2	3
CRAVING FOR TOBACCO_____	☐	☐	☐	☐
IRRITABILITY_____	☐	☐	☐	☐
ANXIETY_____	☐	☐	☐	☐
DIFFICULTY CONCENTRATING_____	☐	☐	☐	☐
RESTLESSNESS_____	☐	☐	☐	☐
HEADACHES_____	☐	☐	☐	☐
DROWSINESS_____	☐	☐	☐	☐
GASTROINTESTINAL TRACT PROBLEMS_____	☐	☐	☐	☐
IMPATIENCE_____	☐	☐	☐	☐
SOMATIC COMPLAINTS_____	☐	☐	☐	☐
INCREASED EATING_____	☐	☐	☐	☐
HUNGER_____	☐	☐	☐	☐
UNUSUAL ALCOHOL INTAKE_____	☐	☐	☐	☐
UNUSUAL CAFFEINE INTAKE_____	☐	☐	☐	☐
SLEEP DISTURBANCE_____	☐	☐	☐	☐

XV. Questionnaire of Smoking Urges (QSU)

NAME: _____ SUBJECT NO. _____.

QUESTIONNAIRE OF SMOKING URGES

	Strongly disagree			Unsure			Strongly agree
	1	2	3	4	5	6	7
Smoking would make me feel very good right now	☐	☐	☐	☐	☐	☐	☐
I would be less irritable right now if I could smoke	☐	☐	☐	☐	☐	☐	☐
Nothing would be better than smoking a cigarette right now	☐	☐	☐	☐	☐	☐	☐
I am not missing smoking right now	☐	☐	☐	☐	☐	☐	☐
I will smoke as soon as I get the chance	☐	☐	☐	☐	☐	☐	☐
I don't want to smoke right now	☐	☐	☐	☐	☐	☐	☐
Smoking would make me less depressed	☐	☐	☐	☐	☐	☐	☐
Smoking would not help me calm down now	☐	☐	☐	☐	☐	☐	☐
If I were offered a cigarette, I would smoke it immediately	☐	☐	☐	☐	☐	☐	☐
Starting now, I could go without a cigarette for a long time	☐	☐	☐	☐	☐	☐	☐
Smoking a cigarette would not be pleasant	☐	☐	☐	☐	☐	☐	☐
If I were smoking this minute, I would feel less bored	☐	☐	☐	☐	☐	☐	☐
All I want right now is a cigarette	☐	☐	☐	☐	☐	☐	☐
Smoking right now would make me feel less tired	☐	☐	☐	☐	☐	☐	☐
Smoking would make me happier now	☐	☐	☐	☐	☐	☐	☐
Even if it were possible, I probably wouldn't smoke now	☐	☐	☐	☐	☐	☐	☐
I have no desire for a cigarette right now	☐	☐	☐	☐	☐	☐	☐

	Strongly disagree			Unsure			Strongly agree
	1	2	3	4	5	6	7
My desire to smoke seems overpowering	☐	☐	☐	☐	☐	☐	☐
Smoking now would make things seem just perfect	☐	☐	☐	☐	☐	☐	☐
I crave a cigarette right now	☐	☐	☐	☐	☐	☐	☐
I would not enjoy a cigarette right now	☐	☐	☐	☐	☐	☐	☐
A cigarette would taste good right now	☐	☐	☐	☐	☐	☐	☐
I have an urge for a cigarette	☐	☐	☐	☐	☐	☐	☐
I could control things better right now if I could smoke	☐	☐	☐	☐	☐	☐	☐
I am going to smoke as soon as possible	☐	☐	☐	☐	☐	☐	☐
I would not feel better physically if I were smoking	☐	☐	☐	☐	☐	☐	☐
A cigarette would not be very satisfying right now	☐	☐	☐	☐	☐	☐	☐
If I had a lit cigarette in my hand I probably wouldn't smoke it	☐	☐	☐	☐	☐	☐	☐
If I were smoking now I could think more clearly	☐	☐	☐	☐	☐	☐	☐
I would do almost anything for a cigarette right now	☐	☐	☐	☐	☐	☐	☐
I need to smoke now	☐	☐	☐	☐	☐	☐	☐
Right now, I am not making plans to smoke	☐	☐	☐	☐	☐	☐	☐

XVI. Pre-Test Questionnaire (PTQ)

NAME: **SUBJECT NUMBER:** .

PRE-TEST QUESTIONNAIRE

(please circle where appropriate)

Have you smoked *anything* in the last 24 hours? Yes / No

If yes, was it: a) cigarettes, b) cigars, c) pipes, d) cannabis with tobacco, or e) cannabis without tobacco?

How many did you smoke?

What time did you smoke the last thing you smoked? : (24-hour clock)

Did you consume any alcohol last night? Yes / No

If yes, can you please write here what it was that you drank, how much you drank, and at what time you finished drinking: _ _ _

XVII. Other Withdrawal Symptoms Scale (OWS)

Name _____ Subject No. _____

OTHER WITHDRAWAL SYMPTOMS

Please circle one number for each item, indicating whether the stated symptom is present, and if so how intensely it is felt. If the stated symptom is not present, please circle "0". If the symptom is present, but only felt very mildly, please circle "1". If the symptom is present and extreme, please circle "9". Of course, feel free to circle any between these guides if that better describes the severity.

	Not present	Mild				Moderate				Severe
Muscle cramps	0	1	2	3	4	5	6	7	8	9
Depressed/sad	0	1	2	3	4	5	6	7	8	9
Painful joints	0	1	2	3	4	5	6	7	8	9
Excessive yawning	0	1	2	3	4	5	6	7	8	9
Hot/cold flushes	0	1	2	3	4	5	6	7	8	9
Trouble getting to sleep	0	1	2	3	4	5	6	7	8	9
Sick to stomach	0	1	2	3	4	5	6	7	8	9
Irritable	0	1	2	3	4	5	6	7	8	9
Runny nose	0	1	2	3	4	5	6	7	8	9
Poor appetite	0	1	2	3	4	5	6	7	8	9
Weak knees	0	1	2	3	4	5	6	7	8	9
Excessive sweating	0	1	2	3	4	5	6	7	8	9
Tense and jittery	0	1	2	3	4	5	6	7	8	9
Watery eyes	0	1	2	3	4	5	6	7	8	9
Abdominal cramps	0	1	2	3	4	5	6	7	8	9
Fitful sleep	0	1	2	3	4	5	6	7	8	9
Chills and goose flesh	0	1	2	3	4	5	6	7	8	9
Backache	0	1	2	3	4	5	6	7	8	9
Bothered by noises	0	1	2	3	4	5	6	7	8	9
Skin clammy and damp	0	1	2	3	4	5	6	7	8	9

XVIII. Profile Of Mood States (POMS)

Initials_____ **Date**_____

Below is a list of words that describe feelings people have. Please read each one carefully. Then place a circle around the answer which best describes HOW YOU ARE FEELING AT THE MOMENT.

The Numbers refer to these phrases:

EXAMPLE
Friendly 0 1 2 3 4

		Not at all	A little	Moderately	Quite a bit	Extremely
1.	Friendly	0	1	2	3	4
2.	Tense	0	1	2	3	4
3.	Angry	0	1	2	3	4
4.	Worn out	0	1	2	3	4
5.	Unhappy	0	1	2	3	4
6.	Clear-headed	0	1	2	3	4
7.	Lively	0	1	2	3	4
8.	Confused	0	1	2	3	4
9.	Sorry for things done wrong	0	1	2	3	4
10.	Shaky	0	1	2	3	4
11.	Listless	0	1	2	3	4
12.	Peeved	0	1	2	3	4
13.	Considerate	0	1	2	3	4
14.	Sad	0	1	2	3	4
15.	Active	0	1	2	3	4
16.	On edge	0	1	2	3	4
17.	Grouchy	0	1	2	3	4
18.	Blue	0	1	2	3	4
19.	Energetic	0	1	2	3	4
20.	Panicky	0	1	2	3	4
21.	Hopeless	0	1	2	3	4
22.	Relaxed	0	1	2	3	4

23.	**Unworthy**	**0**	**1**	**2**	**3**	**4**
24.	**Spiteful**	**0**	**1**	**2**	**3**	**4**
25.	**Sympathetic**	**0**	**1**	**2**	**3**	**4**
26.	**Uneasy**	**0**	**1**	**2**	**3**	**4**
27.	**Restless**	**0**	**1**	**2**	**3**	**4**
28.	**Unable to concentrate**	**0**	**1**	**2**	**3**	**4**
29.	**Fatigued**	**0**	**1**	**2**	**3**	**4**
30.	**Helpful**	**0**	**1**	**2**	**3**	**4**
31.	**Annoyed**	**0**	**1**	**2**	**3**	**4**
32.	**Discouraged**	**0**	**1**	**2**	**3**	**4**
33.	**Resentful**	**0**	**1**	**2**	**3**	**4**
34.	**Nervous**	**0**	**1**	**2**	**3**	**4**
35.	**Lonely**	**0**	**1**	**2**	**3**	**4**
36.	**Miserable**	**0**	**1**	**2**	**3**	**4**
37.	**Muddled**	**0**	**1**	**2**	**3**	**4**
38.	**Cheerful**	**0**	**1**	**2**	**3**	**4**
39.	**Bitter**	**0**	**1**	**2**	**3**	**4**
40.	**Exhausted**	**0**	**1**	**2**	**3**	**4**
41.	**Anxious**	**0**	**1**	**2**	**3**	**4**
42.	**Ready to fight**	**0**	**1**	**2**	**3**	**4**
43.	**Good natured**	**0**	**1**	**2**	**3**	**4**
44.	**Gloomy**	**0**	**1**	**2**	**3**	**4**
45.	**Desperate**	**0**	**1**	**2**	**3**	**4**
46.	**Sluggish**	**0**	**1**	**2**	**3**	**4**
47.	**Rebellious**	**0**	**1**	**2**	**3**	**4**
48.	**Helpless**	**0**	**1**	**2**	**3**	**4**
49.	**Weary**	**0**	**1**	**2**	**3**	**4**

50.	**Bewildered**	**0**	**1**	**2**	**3**	**4**
51.	**Alert**	**0**	**1**	**2**	**3**	**4**
52.	**Deceived**	**0**	**1**	**2**	**3**	**4**
53.	**Furious**	**0**	**1**	**2**	**3**	**4**
54.	**Efficient**	**0**	**1**	**2**	**3**	**4**
55.	**Trusting**	**0**	**1**	**2**	**3**	**4**
56.	**Full of pep**	**0**	**1**	**2**	**3**	**4**
57.	**Bad-tempered**	**0**	**1**	**2**	**3**	**4**
58.	**Worthless**	**0**	**1**	**2**	**3**	**4**
59.	**Forgetful**	**0**	**1**	**2**	**3**	**4**
60.	**Carefree**	**0**	**1**	**2**	**3**	**4**
61.	**Terrified**	**0**	**1**	**2**	**3**	**4**
62.	**Guilty**	**0**	**1**	**2**	**3**	**4**
63.	**Vigorous**	**0**	**1**	**2**	**3**	**4**
64.	**Uncertain about things**	**0**	**1**	**2**	**3**	**4**
65.	**Bushed**	**0**	**1**	**2**	**3**	**4**

XIX. Information Sheet for Lofexidine Study

(University of Bristol headed paper)

Patient Information Sheet - version 1.3 (10/05/01)

TAKING PART IN RESEARCH

Study No: E4912

Study title: A study of the effects of lofexidine on tobacco withdrawal syndrome.

Researcher: Mr. Robert Hayward, University of Bristol; Telephone (0117) 928 8607

You are being invited to take part in a research project. Here is some information to help you decide whether or not to take part. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything you do not understand or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

1. You may or may not receive any direct benefit from taking part in this study. However, information obtained during the course of this study may help us to understand better your condition or illness. It may also help us in selecting treatment for future patients.

2. It is up to you to decide whether to take part or not. If you decide to take part you will be given an information sheet and consent form. Even if you do decide to take part, you are free to withdraw at any time and without giving a reason. This will not affect the standard of care you will receive. Your doctor will not be upset if you decide not to take part.

3. You may be paid travelling expenses for taking part in this study. The study may require you to attend more frequently. You should ask the study doctor or nurse about this.

4. All the information collected about you during the course of the study will be kept strictly confidential. If the study is of a new drug or we need your

permission to allow representatives of the drug companies or perhaps officials from Government or Health Boards/Health Authorities to look at your health records. This is to check the study is being carried out correctly. Any information taken away by these officials will not have your name on it. Any published report of the research will not identify you.

5. Depending on the type of study, your GP will normally be informed that you are taking part. If this is a problem for you, you should discuss it with your study researcher.

6. Sometimes during the course of the study new information becomes available. Your study doctor will talk to you about this and discuss with you whether you want to continue with the study. If you decide to withdraw, the study doctor will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign an updated consent form.

7. If the study is about medical treatment, the study doctor will tell you about the known side effects which are listed on the attached sheet. If you suffer from any of these or any other symptoms you should tell the study doctor next time you meet. If you are at all worried you should contact the study doctor immediately.

8. Some tests could affect your ability to obtain insurance. You should be sure to ask your study doctor about this.

9. If you have private medical insurance you should let the insurers know that you intend to take part in a research project. They will be able to tell you if this will affect your medical insurance.

10. Consumers for ethics in research (CERES) publish a leaflet entitled 'Medical Research and You'. This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London N16 0BW.

1. Study title

A repeated measures placebo-controlled study of the effect of lofexidine on the tobacco withdrawal syndrome compared with nicotine replacement.

Repeated measures means that there are no distinct groups in the study – each participant will perform all parts of the study. *Placebo* means a dummy medication such as a pill which looks like the real thing but contains no active ingredient.

2. What is the purpose of the study?

This study will attempt to examine whether a drug – lofexidine – can help ease withdrawal symptoms associated with stopping smoking and perhaps therefore make cigarette smoking easier to give up. Smoking is difficult to give up because people can become addicted to the nicotine delivered in cigarettes. When your body and brain becomes accustomed to a particular

level of nicotine, it can often give you signals (e.g. craving) when your blood nicotine levels fall below that to which it has become accustomed. This is known as *withdrawal.*

These symptoms can be unpleasant, and tend to drive people to seek nicotine: i.e. smoke. This is referred to as *nicotine dependence.* The most common withdrawal symptoms associated with smoking cessation are: craving for tobacco, irritability, anxiety, difficulty concentrating, restlessness, headaches, drowsiness, gastrointestinal tract [digestive] problems, impatience, somatic [bodily] complaints, increased eating, hunger, unusual alcohol intake, unusual caffeine intake and sleep disturbance.

The most effective way of treating these effects is with nicotine – but this maintains the dependence, thereby proving problematic when attempting to quit smoking. Alternative ways of assisting people trying to give up smoking are therefore important, and several substances have been looked at in this capacity. Clonidine, a drug that works in a similar way to lofexidine, has been shown by some studies to help relieve the withdrawal symptoms of smoking cessation. Lofexidine itself has been successfully used to treat the withdrawal symptoms of other addictive drugs.

We wish to investigate whether the effects of lofexidine can relieve nicotine withdrawal symptoms like those mentioned. We hope that, should our findings be positive, lofexidine could then be developed as a useful tool allowing people a more effective passage to stopping smoking, and thereby reduce people's likelihood of contracting lung cancer, heart disease, and other smoking-related illnesses. We will achieve this by comparing how abstinent smokers administered lofexidine differ from abstinent smokers treated with placebo, and whether these effects can compare favourably with nicotine replacement.

3. Why have I been chosen?

You have been invited to participate because you are a smoker that has either: *a)* expressed an interest in doing research of this kind in the past, or *b)* because you have responded to an advertisement asking for volunteers for this study. You should not take part in this study if you have a history of serious medical or psychiatric illness, or if you are a non-smoker or "part-time" smoker.

4. Who is organising the study

The study is being organised by the Psychopharmacology Unit at the University of Bristol, School of Medical Sciences. It is expected to run for a total of approximately 4 months, during which time we would like you to attend during two experimental weeks. During these weeks you will be asked to attend on a Monday (9:00am-9:30am), Tuesday (9:00am-11:00am) and Friday (9:00am-11:00am)

5. What will happen to me if I take part?

Initially we will ask you to complete a questionnaire asking you about yourself, your health and your smoking behaviours – you may complete this is your own time. Providing you fulfil the criteria for taking part in this study, you will then be asked to attend the Clinic six times during 2 (not necessarily consecutive) experimental weeks, for a period of either 30 minutes or 2 hours. If you are able and willing to commit these times, you will be invited to attend the Clinic at 9.00am on a Monday (Week 1) for your first experimental session.

You will be asked to smoke as you would normally right up to the time you arrive at the Clinic. Upon arrival you will be asked to complete questionnaires regarding your mood, smoking urges, various psychological and physical items relating to tobacco withdrawal. Once these are completed, you will be asked to complete a battery of mental performance tests (measuring attention, reaction times and visual vigilance) which will be presented on a computer screen. You

will then be free to leave the Clinic at approximately 9.30am, but directed to NOT SMOKE for the following 24 hours.

You will be asked to return the Clinic the following day (Tuesday, Week 1) where you will complete the same questionnaires and computer tasks again. Following these, you have an hour break in which to read, etc. during which time you will be given your medication. In the first week you will receive either lofexidine (or a placebo) in tablet form or nicotine (or a placebo) in an inhalator. If you receive a tablet, you will be receiving pill containing 0.2mg lofexidine or a lactose placebo at approximately 9.30am. If you receive the inhalator you will be infusing approximately 10mg nicotine or a menthol placebo at approximately 10.00am. At 10.30am, you will again be asked to complete the same questionnaires and perform the computer tasks again.

You will then be free to leave the Clinic at approximately 11.00am. You may then smoke normally until 9.00am on Thursday morning after which time you must again NOT SMOKE for 24 hours. You will then be asked to return to the Clinic on Friday at 9.00am where you will perform the same procedure as the Tuesday, with the exception of receiving the placebo/drug reverse of that administered earlier in the week.
Week 2 will be the same procedure as Week 1 except that if you received lofexidine in Week 1 you will receive nicotine in Week 2 and vice versa.

6. What is the drug?

Lofexidine is a drug that acts in the brain, reducing the amount released of a particular chemical messenger [noradrenaline]. Currently its only clinical use is for the alleviation of symptoms in patients undergoing a detoxification from opiate drugs. It is unlikely that you would suffer any side effects from the single tablet containing a low dose we are using.

Possible side effects are drowsiness, dry mucous membranes [particularly mouth, nose and throat], lowered blood pressure, slowed heart rate, and slight possibility of rebound hypertension on withdrawal. We would also advise you NOT TO DRIVE while taking this medication.

7. Are there other ways of treating my condition?

A number of medications are currently utilised in the treatment of tobacco withdrawal. Nicotine replacement therapy (NRT) such as patches, gum and inhalators/nasal sprays are readily available, and a new drug – Zyban (bupropion) – are established tools used for alleviating withdrawal symptoms associated with stopping smoking.

8. Are there any disadvantages in taking part in this study?

Possible side effects of lofexidine are drowsiness, dry mucous membranes [particularly mouth, nose and throat], lowered blood pressure, slowed heart rate, and slight possibility of rebound hypertension on withdrawal. Subjects are advised not drive following administration of lofexidine. A doctor will be readily accessible in case of any adverse event. The most common withdrawal symptoms associated with smoking cessation are: craving for tobacco, irritability, anxiety, difficulty concentrating, restlessness, headaches, drowsiness, gastrointestinal tract [digestive] problems, impatience, somatic [bodily] complaints, increased eating, hunger, unusual alcohol intake, unusual caffeine intake and sleep disturbance.

9. What are the possible risks of taking part?

It is possible that lofexidine-induced lowered blood pressure may result in slight dizziness or feeling faint.

10. What are the possible benefits of taking part?

You will receive £75 upon satisfactory completion. If you partially complete the study to some useful degree (e.g. only complete 1 experimental week) you will receive £30. Aside from the financial reward for taking part, we hope that both nicotine and lofexidine can be shown to

alleviate tobacco withdrawal symptoms. However, this cannot be guaranteed. The information we get from this study may help understand nicotine withdrawal better, and may suggest a possible for use for lofexidine as a tool for helping people trying to quit smoking.

11. Is my doctor being paid for including me in the study?

No.

12. What happens when the trial stops?

Lofexidine will not be available, however NRT is available over-the-counter from pharmacies.

13. Are there any restrictions on what I might eat or do?

Avoid alcohol in the 24 hours prior to attending the Clinic on each day.

14. What if something goes wrong?

Compensation for any injury caused by taking part in this study will be in accordance with the guidelines of the University of Bristol "No Fault" Compensation scheme. Copies of these guidelines are available on request.

15. Confidentiality – who will know I am taking part in the study?

Any confidential or personal information will only be made available to researchers who are involved in this study.

16. GP Notification

As you are a healthy volunteer, there is no reason why your GP should be notified of your involvement in this project, although you may wish to inform him or her yourself.

17. LREC Approval

The United Bristol Healthcare Trust Ethics Committee has approved this study.

18. What will happen to the results of the study?

Subjects will be fully debriefed on completion of the study, and results will be made available as and when requested for individual subjects, or later in the year (August/September) for results of the study in general.

19. Contact for further information

If you, your friends or relatives have any questions about this project, please contact Mr Robert Hayward on (0117) 925 3066.

XX. Consent Form for Lofexidine study

(University of Bristol headed paper)

Centre number:

Study number: E4912

Patient information number for this trial:

CONSENT FORM

Title of Project: A repeated measures placebo-controlled study of the effect of lofexidine on the tobacco withdrawal syndrome compared with nicotine replacement.

Name of Researcher: Mr Robert Hayward

Please initial box

1. I confirm I have read and understand the information sheet dated 10/05/01 (version1.3) for the above study ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected ☐
3. I am willing to allow access to my medical records but understand that strict confidentiality will be maintained. The purpose of this is to check that the study is being carried out correctly. ☐
4. I agree to take part in the above study. ☐

Name of patient	Date	Signature
Name of person taking consent (if different to researcher)	Date	Signature
Researcher	Date	Signature

1 for patient, 1 for researcher, 1 to be kept with hospital notes.